oxalic acid to give the oxalate, mp 164–168°. The analytical sample from EtOH had mp 166–176°. *Anal.* ($C_{23}H_{23}Cl_2NO_4$) C, H, N.

Acknowledgments. We express our appreciation to Dr. Joe Potts and Jim Blass for the pharmacological assays, Dr. Roy Bible for nmr interpretations, and Mr. E. Zielinski for microanalytical results.

References

(1) B. Blackwell, J. O. Lipkin, J. H. Meyer, R. Kuzma, and W. V. Boulter, *Psychopharmacologia*, **25**, 205 (1972).
(2) R. F. Childs and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 6348 (1967).
(3) W. E. Coyne and J. W. Cusic, U. S. Patent 3,547,933 (1970).
(4) I. Lapin, *Psychopharmacologia*, 11, 79 (1967).

Synthesis and Antimalarial Effects of 1-(3,4-Dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine and Related Substances†,‡

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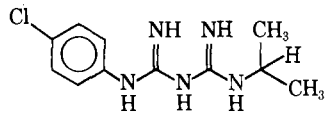
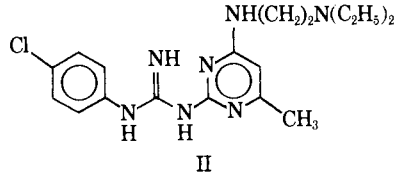
One hundred and twenty-one 1-aryl-3-[4-[[(mono- and dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines (VIII) were synthesized by the condensation of the requisite 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-arylguanidine (VII) with the appropriate polyamine in EtOH, HOAc, or C_6H_5Cl in the presence of NaOH. The 1-(4-hydroxy-6-methyl-2-pyrimidinyl)-3-arylguanidine precursors (VI), prepared by the condensation of a substituted aniline with 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine (V) or *via* an arylbiguanide (IV) and a β-keto ester, were readily converted to the chloropyrimidines VII utilizing $POCl_3$. Ninety of the new pyrimidinylguanidines possessed "curative" activity against *Plasmodium berghei* at single subcutaneous doses ranging from 20 to 640 mg/kg, and nearly all of them were less toxic for mice than the reference drug 1-(*p*-chlorophenyl)-3-[[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidine (II). Orally, 62 compounds exhibited suppressive activity against *P. berghei* comparable with or superior to II, while 46 of them were 2 to 30 times as potent as quinine hydrochloride. Fifty-nine compounds also displayed strong suppressive activity against *P. gallinaceum* in chicks, 17 of which "cured" chicks at single subcutaneous doses of 60–320 mg/kg. One of the more promising compounds, 1-(3,4-dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine (61), possessed strong activity against cycloguanil- and DDS-resistant lines of *P. berghei* and was designated for preclinical toxicological studies and clinical trial. Structure–activity relationships are discussed.

During the evolutionary process that led to the development of chlorguanide (I),[2,3] it was discovered that various 1-phenyl-3-(4-amino-2-pyrimidinyl)guanidines possessed strong antimalarial effects against *Plasmodium gallinaceum* in chicks.[4] One of the most potent members of the



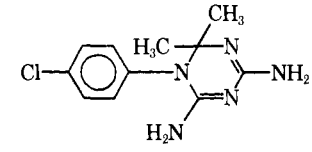
I

series, namely 1-(*p*-chlorophenyl-3-[4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidine (II),[4,5] proved to be roughly equivalent to quinacrine in antimalarial potency and toxicity and was therefore selected for expanded chemotherapeutic studies and clinical trial.[6]



II

Compound II was subsequently shown to be effective against *P. cathemerium* and *P. relictum* in canaries,[6] *P. knowlesi* in rhesus monkeys,[7] and *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* in man.[6,8-11] However, this drug and related pyrimidinylguanidine derivatives were not pursued further with the advent of chlorguanide and its active metabolite, cycloguanil (III).



III

Curd, Davey, and Rose advanced the working hypothesis that the antimalarial activity of chlorguanide and its precursors might be associated with the linking of an aryl group and the amidine moiety $-N{=}C{-}N{=}C{-}NHR_1$ through groupings capable of prototropic change.[12] Since this structural feature is common to all the compounds that exhibited activity, whether pyrimidines of the type II or biguanides of type I, it was reasonable to postulate that the ultimate mechanism of parasiticidal action should be shared by all these compounds. It was, therefore, tacitly assumed that strains of malarial parasites that are resistant to chlorguanide (I) would also be cross-resistant to the pyrimidinylguanidine II and related substances. Subsequent studies demonstrated conclusively that this is not the case. Thus, no cross resistance was observed when II was tested against a strain of *P. gallinaceum* that was resistant (20–40-fold) to chlorguanide,[13,14] a strain of *P. berghei* that was resistant (100-fold) to sulfadiazine and cross-resistant with chlorguanide,[15] and strains of *P. knowlesi* that were resistant to chlorguanide (2400-fold)[7] and pyrimethamine (>2 × 10^6-fold).[16] Furthermore, when a normal drug-sensitive strain of *P. gallinaceum* was subjected for nearly 2.5 years to intensive treatment with II, no drug resistance was acquired.[13,14]

When confronted in 1965 with the challenge of devel-

†This is communication 35 of a series on antimalarial drugs. For paper 34, see ref 1.

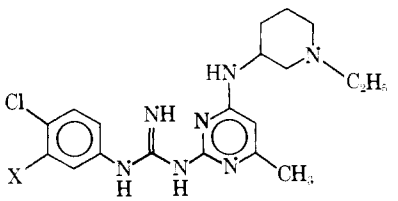
‡This investigation was supported by U. S. Army Medical Research and Development Command Contract DA-49-193-MD-2754. This is Contribution No. 1092 to the Army Research Program on Malaria.

§This paper is dedicated in tribute to Professor Alfred Burger—esteemed teacher, scientist, editor, and friend.

oping new agents that might be useful against drug-resistant malarias,[3] we were impressed with the reported performance of II against chlorguanide-, pyrimethamine-, and sulfadiazine-resistant plasmodia[7,13-16] and seized upon this lead as one that warranted reinvestigation. In this regard, it is noteworthy that Cliffe and coworkers[17] in 1948 reported the synthesis and antimalarial effects of a large group of congeners of II. These authors concluded that none of the analogs they prepared possessed enhanced activity over II.[17]

As a prelude to the present study, a sample of II (2, Table I) was resynthesized[4] to enable the acquisition of base line data against both sensitive and drug-resistant plasmodia in contemporary test systems.[18-22] In a preliminary experiment, 2 base was administered by gavage twice daily for 4 days to mice infected with the parent (P) drug-susceptible strain of *P. berghei* and another strain (T) that was approximately 30-fold resistant to cycloguanil hydrochloride.[18] The SD_{90} (daily dose required for 90% suppression of the parasitemia in treated mice relative to control mice) against the P and T strains was 28 and 27 mg/kg per day, respectively. The relative quinine equivalents (Q) (the ratio of the SD_{90} of quinine hydrochloride to the SD_{90} of the test substance) were 2.6 and 2.7. A subsequent experiment was done utilizing the T and PYR lines when they were >300-fold resistant, respectively, to cycloguanil hydrochloride and pyrimethamine.[18,19] In this study, 2 was given orally to mice by drug diet for 6 days. The SD_{90} was estimated to be 68 mg/kg per day (Q = 1.1) for the susceptible line P, 69 mg/kg per day (Q = 1.1) for the cycloguanil-resistant line T, and 63 mg/kg per day (Q = 1.2) for the pyrimethamine-resistant line PYR. The results of both of these studies were consistent with earlier reports[7,13-16] that there is no apparent cross resistance between 2 and folate antagonists such as chlorguanide, cycloguanil, and pyrimethamine. Moreover, antimetabolite studies conducted in these laboratories showed that 2 lacked appreciable antifolate activity. Thus 50% inhibition of *Streptococcus faecalis* R (*Strep. faecium* var. *durans*, ATCC 8043)[21] by the guanidinopyrimidine 2 required 750,000 ng/ml, while cycloguanil hydrochloride and pyrimethamine produced 50% inhibition at concentrations of 8 and 4 ng/ml, respectively.[21] The inhibitory effects of 2 were not reversed by folic acid.

The present communication summarizes the results of an extensive investigation into the synthesis and antimalarial properties of an array of new guanidinopyrimidines. Many of these substances proved to be considerably more active against *P. berghei* and less toxic for mice than 2, and one substance, namely 1-(3,4-dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine (61), was designated for preclinical toxicological studies[23] and clinical trial.[24,*]

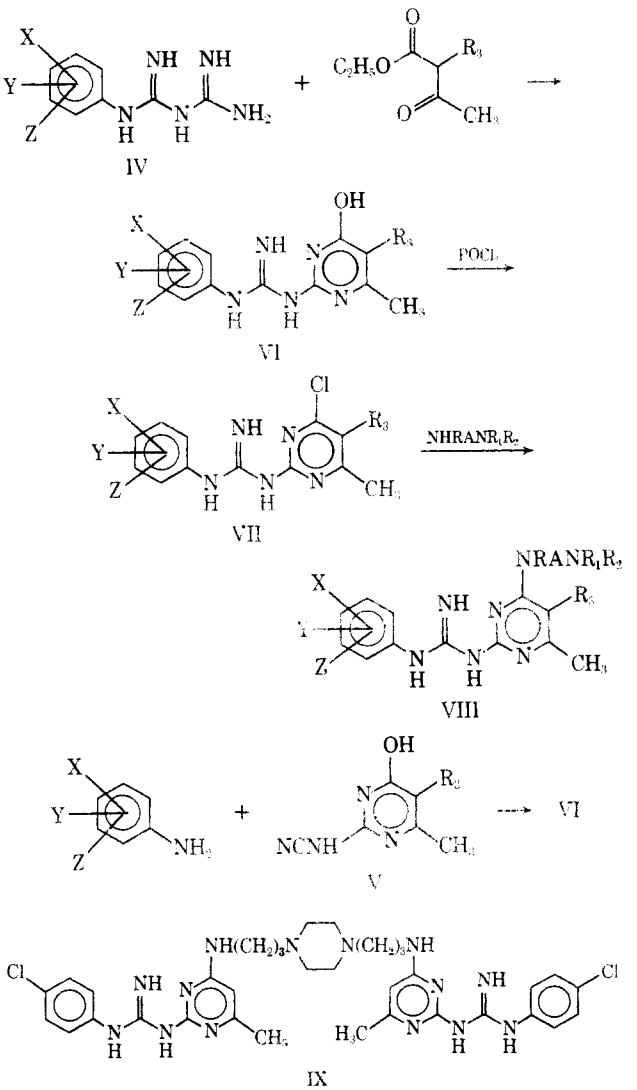


5, X = H

61, X = Cl

Chemistry. The 1-(substituted phenyl)-3-[4-[[(alkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines (VIII) (1-123, Tables I and II) were synthesized according to the general route depicted in Scheme I utilizing modifications of the procedures described previously.[4,17] Thus the requisite 1-(4-hydroxy-6-methyl-2-pyrimidinyl)-3-(substituted phenyl)guanidine (VI), obtained either by the condensation of a substituted aniline with 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine (V, R_3 = H) or *via* an arylbiguanide (IV) and a β-keto ester, was chlorinated with $POCl_3$ to give the appropriate 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(substituted phenyl)guanidine (VII, 20-100% yield). Treatment of the 4-chloropyrimidines (VII) with a polyamine side chain in refluxing acidic EtOH (method A), in HOAc (method B), or most commonly in refluxing C_6H_5Cl in the presence of NaOH (method C) afforded the desired aminopyrimidines (VIII) (1-123, Tables I and II) in 1-79% yield. 1,1'-[1,4-Piperazinediylbis[trimethyleneimino(6-methyl-4,2-pyrimidinediyl)]]bis[3-(*p*-chlorophenyl)guanidine] (IX) was obtained in poor yield (8%) from 2 equiv of 1-(*p*-chlorophenyl)-3-(4-chloro-6-methyl-2-pyrimidinyl)guanidine and 1 equiv of 1,4-bis(3-aminopropyl)piperazine.

Scheme I



The attempted reaction between 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine and 3-amino-1-ethylpiperidine in DMF in the presence of NaH gave, instead of the desired product, the dimethylamino compound 77. The same chloro compound treated with 4-amino-2-[(diethylamino)methyl]-1-naphthol provided, instead of the desired product, the diethylamino derivative

[*] E. A. Steck, Walter Reed Army Institute of Research, private communication, 1968.

78 which apparently resulted from decomposition of the Mannich intermediate. Spectral data (ir, uv, and nmr) were in agreement with the structures assigned for each of the guanidinopyrimidines.

Suppressive Antimalarial Screening in Mice. The 1-aryl-3-(4-amino-6-methyl-2-pyrimidinyl)guanidines 1–8, 10–55, and 57–123 (Tables I and II) and IX described in the present communication were tested initially against a normal drug-sensitive strain of *P. berghei* in mice by the parenteral route.**,†† The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 hr postinfection. Extension of the mean survival time of the treated mice is interpreted as evidence of antimalarial activity.[20] 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 III–XVIII.

The vast majority of these pyrimidinylguanidines was also evaluated orally against another normal drug-sensitive strain of *P. berghei* in mice.‡‡,§§ The drugs were given continuously in the diet of mice for 6 consecutive days, and all drug doses were calculated as free base equivalent. Results (Tables III–XVIII) are expressed both in terms of the SD_{90} and the quinine equivalent Q.

Both oral and parenteral base line data for the reference drugs 1-(*p*-chlorophenyl)-3-[4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidine (II, **2**), quinine, and cycloguanil hydrochloride (III) are included for comparative purposes (Table III).

Although **2** displayed respectable antimalarial activity against *P. berghei* in mice when administered orally either by gavage (Q = 2.6) or by drug diet (Q = 1.1) and was tolerated well (*vide supra*), the drug showed unexpected toxicity for mice when given subcutaneously. Thus **2** killed mice after single subcutaneous doses of 80, 160, and 640 mg/kg and exhibited significant activity at only one nontoxic dose level, namely at 40 mg/kg (Table III). None of the animals was cured at any dose level.

Overall Results and Structure–Activity Relationships in Mice. Fortuitously, two favorable structural modifications were effected in the early stages of this investigation that had a profound effect on overall strategy. First of all, it was discovered that the replacement of the 4-[[2-(diethylamino)ethyl]amino] side chain of **2** with a 4-[(1-ethyl-3-piperidyl)amino] moiety afforded a compound (**5**) that, when administered subcutaneously, was nontoxic for mice and displayed curative activity against *P. berghei* at doses ranging from 80 to 640 mg/kg (Table III). However, compound **5** showed no superiority over **2** when administered orally by drug diet. Secondly, it was found that 1-(3,4-dichlorophenyl)-3-[4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidine (**14**), wherein a second chlorine atom was introduced at position 3 in the benzene ring, was significantly more active than **2** against *P. berghei* by both routes of administration and was less toxic for mice subcutaneously (Table IV). Thus, **14** was nearly four times as potent (Q = 4.2) as **2** orally, and subcutaneously the drug increased the mean survival time of mice 7.3 days at 20 mg/kg and displayed curative effects at 40–640 mg/kg.

Oral antimalarial potency was further enhanced when these two structural parameters were combined in 1-(3,4-dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine (**61**). The SD_{90} of **61** against *P. berghei* in mice by drug diet was 7 mg/kg per day (Q = 11), and the drug was tolerated well. Subcutaneously, **61** effected a significant increase in the mean survival time of mice at 20 mg/kg and cured mice at doses ranging from 40 to 640 mg/kg (Table XI). Only three toxic deaths occurred among 20 mice treated at the highest dose level, 640 mg/kg.

In yet a third study utilizing *P. berghei* in mice, **61** was administered to mice subcutaneously once daily for 3 days starting on the day of inoculation.[23] Results showed that **61** in doses of 2.5, 5, 10, 25, 50, and 100 mg/kg per day completely suppressed parasitemia on day 6 after inoculation. Relative to standard drugs, compound **61** was estimated to be about 100 times more active than quinidine and 10 times more active than **2**.[23]

The above findings stimulated an extensive investigation of structure–activity relationships in this series. Unlike **2**, 90 of the new pyrimidinylguanidines possessed curative effects subcutaneously. Moreover, 54 substances (**5**, **14–20**, **22**, **25**, **28**, **31–34**, **38**, **42**, **44**, **46**, **47**, **49**, **50**, **59–66**, **83–88**, **92**, **93**, **95**, **97–100**, **102–107**, and **110–114**) were equipotent with or more potent than **2** at low dose levels where **2** was not toxic, and nearly all of these new compounds were less toxic for mice than **2**. Among 95 compounds tested by the oral route, 62 exhibited antimalarial activity comparable with or superior to **2**, and 16 (**15**, **17**, **32**, **37**, **38**, **42**, **44**, **61**, **69**, **83**, **97**, **98**, **100**, **102**, **104**, and **110**) were 5 to 27 times more potent then **2** (Tables III–XVIII). In general, there was a remarkably good correlation between subcutaneous and oral test results in mice.

An analysis of these results leads to the following generalizations concerning structure–activity relationships.

(1) Optimal activity and favorable toxicity patterns are encountered when the aryl substituents are 3,4-dichlorophenyl, 3,5-dichlorophenyl, and 4-halo-α,α,α-trifluoro-*m*-tolyl (Tables IV, VII–XII, and XIV–XVII *vs.* Table III).

(2) The introduction of MeO, Bu, or benzyloxy substituents in the benzene ring abolishes activity (**116**, **118**, **119**, **122** *vs.* **2**).

(3) Activity is diminished when a 1-naphthyl moiety is substituted for phenyl (**120**, **123** *vs.* **5**, **13**).

(4) Insertion of a methylene bridge between the phenyl group and the guanidine function results in the loss of antimalarial activity (**117** *vs.* **18**).

(5) Replacement of H with Me or benzyl at position 5 of the pyrimidine ring leads to a diminution or loss of antimalarial effects (**115**, **121** *vs.* **14**).

(6) A basically substituted side chain is essential for significant activity (**77–79** *vs.* **14**).

(7) Removal of one alkyl group from the distal side chain nitrogen leads to a substantial reduction in activity and often to an increase in toxicity (Table V). This effect is especially noteworthy since these 1-(3,4-dichlorophenyl)-3-[4-[[(monoalkylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidines, by analogy with chloroquine,[3] represent likely metabolites of the parent dialkylamino substances.

(8) Side-chain hydroxylation leads to a marked reduction in activity and, surprisingly, to an increase in toxicity (Table VI) (*cf.* hydroxychloroquine[3]).

(9) Side-chain branching is usually favorable (Table VII).

(10) Potent activity is usually retained when the proximal amine of the side chain is tertiary (Table VIII).

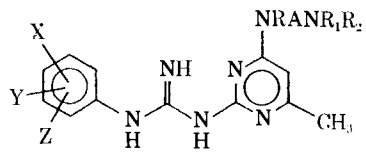
**The parenteral antimalarial screening in mice was carried out by Dr. Leo Rane of the University of Miami, and test results were provided through the courtesy of Dr. T. R. Sweeney and Dr. E. A. Steck of the Walter Reed Army Institute of Research.

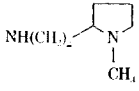
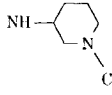
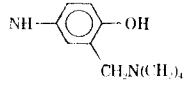
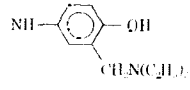
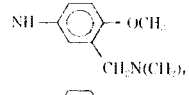
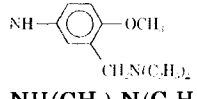
††For a description of the test method, see ref 20.

‡‡The oral antimalarial screening against *P. berghei* in mice was carried out by Dr. Paul E. Thompson and coworkers, Department of Pharmacology, Parke, Davis and Co., Ann Arbor, Mich.

§§For a description of the test method, see ref 18 and 19.

Table I. 1-(Substituted phenyl)-3-[4-[[(mono- and dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl] guanidines



No.	X, Y, Z	NRANR$_1$R$_2$	Procedure	Mp, °C	Yield, purified, %	Purifcn solvent	Formula	Analyses
1	4-Cl	$N[(CH_2)_2]_2NCH_3$	A	174–175	35	Et_2O	$C_{17}H_{22}ClN_7$	C, H, N
2	4-Cl	$NH(CH_2)_2N(C_2H_5)_2$	B	155–156[m]	30	EtOH–H_2O	$C_{18}H_{26}ClN_7$	C, H, N
3	4-Cl	$NH(CH_2)_3N(CH_2)_4$	B	207–208	32	EtOH–H_2O	$C_{19}H_{26}ClN_7$	C, H, N
4	4-Cl		A	201–202	29	EtOH	$C_{19}H_{26}ClN_7$	C, H, N
5	4-Cl		A	191–192.5	23	MeCN	$C_{19}H_{26}ClN_7$	C, H, N
6	4-Cl	1-NH-4-N$(CH_3)_2C_6H_{10}$	A	223–224	28	MeCN	$C_{20}H_{28}ClN_7$	C, H, N
7	4-Cl	$NH(CH_2)_2N[CH(CH_3)_2]_2$	A	186–187	57	EtOH–H_2O	$C_{20}H_{30}ClN_7$	C, H, N
8	4-Cl	$NH(CH_2)_3N(CH_2)_6$	B	183–185	24	EtOH–H_2O	$C_{21}H_{30}ClN_7$	C, H, N
9	4-Cl	1-NH-4-N$(C_2H_5)_2C_6H_{10}$	C	185–188	1	MeCN	$C_{22}H_{32}ClN_7$	C, H, N
10	4-Cl		A	245–246	18	DMF–H_2O	$C_{23}H_{26}ClN_7O$	C, H, N
11	4-Cl		A	217 dec	37	DMF–H_2O	$C_{23}H_{28}ClN_7O$	C, H, N
12	4-Cl		A	218–220	56	DMF–H_2O	$C_{24}H_{28}ClN_7O$	C, H, N
13	4-Cl		A	181–182	74	EtOH–H_2O	$C_{24}H_{30}ClN_7O$	C, H, N
14	3,4-Cl_2	$NH(CH_2)_2N(C_2H_5)_2$	A	141–142.5	67	EtOH–H_2O	$C_{18}H_{25}Cl_2N_7$	C, H, N
15	3,4-Cl_2	$NH(CH_2)_2N(CH_3)(CH_2)_3CH_3$	C	114–115	74	MeCN	$C_{19}H_{27}Cl_2N_7$	C, H, N
16	3,4-Cl_2	$NH(CH_2)_2N(CH_2CH{=}CH_2)_2$	C	139–140	49	MeCN	$C_{20}H_{25}Cl_2N_7$	C, H, N
17	3,4-Cl_2	$NH(CH_2)_2N(C_2H_5)(CH_2)_3CH_3$	C	116–118	73	MeCN	$C_{20}H_{29}Cl_2N_7$	C, H, N
18	3,4-Cl_2	$NH(CH_2)_2N[CH(CH_3)_2]_2$	C	178–180	71	MeCN	$C_{20}H_{29}Cl_2N_7$	C, H, N
19	3,4-Cl_2	$NH(CH_2)_2N[(CH_2)_3CH_3]_2$	C	137–139	74	MeCN	$C_{22}H_{33}Cl_2N_7$	C, H; N[b]
20	3,4-Cl_2	$NH(CH_2)_2N[CH(CH_3)C_2H_5]_2$	C	182–183	75	MeCN-C_6H_6	$C_{22}H_{33}Cl_2N_7$	C, H, N
21	3,4-Cl_2	$NH(CH_2)_2NHC_2H_5$	C	250–255 dec	5	EtOH	$C_{16}H_{21}Cl_2N_7 \cdot 1.5HCl \cdot 2.7H_2O$	C, N, Cl, H_2O; H[b]
22	3,4-Cl_2	$NH(CH_2)_2NHCH_2CH{=}CH_2$	C	115–118	5	MeCN–*i*-PrOH	$C_{17}H_{21}Cl_2N_7$	C, H, N
23	3,4-Cl_2	$NH(CH_2)_2NHCH(CH_3)_2$	C	175–178	8	MeCN–*i*-PrOH	$C_{17}H_{23}Cl_2N_7 \cdot HCl \cdot H_2O$	C, H, N, Cl, H_2O

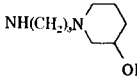
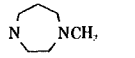
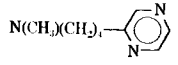
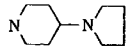
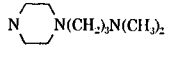
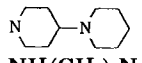
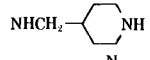
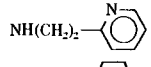
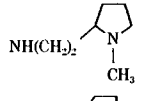
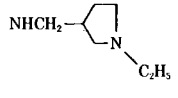
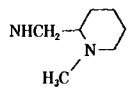
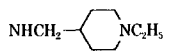
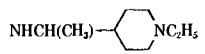
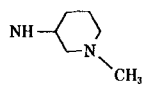
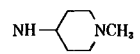
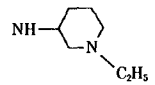
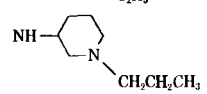
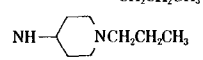
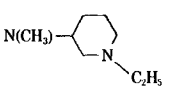
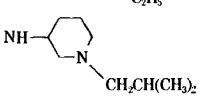
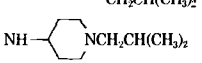
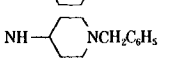
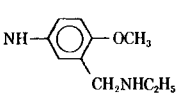
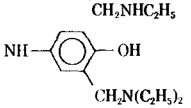
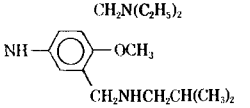
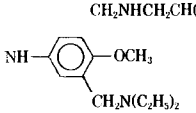
24	3,4-Cl_2	$NH(CH_2)_2NHCH_2CHOHCH_3$	C	136–144	10	$C_6H_5CH_3$	$C_{17}H_{23}Cl_2N_7O$	C, H, N
25	3,4-Cl_2	$NH(CH_2)_2NHCH(CH_3)C_2H_5$	C	71–81	9	MeCN–*i*-PrOH	$C_{18}H_{25}Cl_2N_7 \cdot 0.1H_2O$	C, H, N, H_2O
26	3,4-Cl_2	$NH(CH_2)_2NHCH_2COH(CH_3)_2$	C	169–172	36	MeCN	$C_{18}H_{25}Cl_2N_7O$	C, H, N
27	3,4-Cl_2	$NH(CH_2)_2N(C_2H_5)(CH_2)_2OH$	C	115–118	30	MeCN	$C_{18}H_{25}Cl_2N_7O$	C, H, N
28	3,4-Cl_2	$NHCH_2CHOHCH_2N(C_2H_5)_2$	C	197–207	30		$C_{19}H_{27}Cl_2N_7O \cdot 2.8HCl$	C, H, N, Cl
29	3,4-Cl_2		C	138–140	28	MeCN	$C_{20}H_{27}Cl_2N_7O$	C, H, N
30	3,4-Cl_2	$NH(CH_2)_2N(C_2H_5)CH_2COH(CH_3)_2$	C	154–155	71	MeOH–H_2O	$C_{20}H_{29}Cl_2N_7O$	C, H, N
31	3,4-Cl_2	$NHCH(CH_3)CH_2N(CH_3)_2$	C	131–133	36	MeCN	$C_{17}H_{23}Cl_2N_7$	C, H, N
32	3,4-Cl_2	$NHCH_2CH(CH_3)N(CH_3)_2$	A	142–144	18	MeCN	$C_{17}H_{23}Cl_2N_7$	C, H, N
33	3,4-Cl_2	$NHCH(CH_3)CH_2N(C_2H_5)_2$	C	108–113	23	*n*-Heptane	$C_{19}H_{27}Cl_2N_7$	C, H, N
34	3,4-Cl_2	$NHCH_2CH(CH_3)N(C_2H_5)_2$	C	128–130	79	MeCN	$C_{19}H_{27}Cl_2N_7$	C, H, N
35	3,4-Cl_2	$1\text{-}NH\text{-}4\text{-}N(CH_3)_2C_6H_{10}$	A	238–240	9	EtOH–H_2O	$C_{20}H_{27}Cl_2N_7$	C, H, N
36	3,4-Cl_2	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	C	60–70	42		$C_{21}H_{31}Cl_2N_7 \cdot 0.3H_2O$	C, H, N, H_2O
37	3,4-Cl_2	$NHCH_2C(CH_3)_2CH_2N(C_2H_5)_2$	C	165–170	12	Me_2CO	$C_{21}H_{31}Cl_2N_7 \cdot HCl \cdot H_2O$	C, H, N, Cl; H_2O[c]
38	3,4-Cl_2	$NHCH(CH_3)CH_2N(CH_2CH_2CH_3)_2$	C	150–155	9	EtOAc	$C_{21}H_{31}Cl_2N_7 \cdot HCl \cdot H_2O$	C, H, N, Cl, H_2O
39	3,4-Cl_2	$1\text{-}NH\text{-}4\text{-}N(C_2H_5)_2C_6H_{10}$	C	182–186	16	MeCN	$C_{22}H_{31}Cl_2N_7$	C, H, N
40	3,4-Cl_2		C	135–137	32	MeCN	$C_{18}H_{23}Cl_2N_7$	C, H, N
41	3,4-Cl_2	$N(CH_3)CH_2CH(CH_3)N(CH_3)_2$	C	258–261	9	EtOH	$C_{18}H_{25}Cl_2N_7 \cdot 2HCl$	C, N; H[d]
42	3,4-Cl_2	$N(CH_3)(CH_2)_2N(C_2H_5)_2$	C	205–207	34		$C_{19}H_{27}Cl_2N_7 \cdot 2HCl \cdot H_2O$	C, H, N, Cl^-, H_2O
43	3,4-Cl_2		C	145–147	41	MeCN	$C_{21}H_{24}Cl_2N_8$	C, H, N
44	3,4-Cl_2		A	224–230	33	MeOH	$C_{21}H_{27}Cl_2N_7 \cdot 2HCl \cdot 0.86H_2O$	C, H; N, Cl^-, H_2O[e]
45	3,4-Cl_2		C	172–178	4		$C_{21}H_{30}Cl_2N_8 \cdot 2HCl \cdot 1.3H_2O$	C, H, N, Cl, H_2O
46	3,4-Cl_2		A	240–250	4	*i*-PrOH	$C_{22}H_{29}Cl_2N_7 \cdot 2HCl \cdot 3H_2O$	H, N, Cl^-, H_2O; C[f]
47	3,4-Cl_2	$NH(CH_2)_2N(CH_2)_4$	C	151–154	42	MeCN	$C_{18}H_{23}Cl_2N_7$	C, H, N
48	3,4-Cl_2	$NH(CH_2)_3N(CH_2)_4$	A	201–202	16	EtOH	$C_{19}H_{25}Cl_2N_7$	C, H, N
49	3,4-Cl_2	$NH(CH_2)_2N(CH_2)_5$	C	166–169	22	MeCN	$C_{19}H_{25}Cl_2N_7$	C, H, N
50	3,4-Cl_2	$NH(CH_2)_2N(CH_2)_6$	C	167–170	24	MeCN	$C_{20}H_{27}Cl_2N_7$	C, H, N
51	3,4-Cl_2	$NH(CH_2)_3N(CH_2)_6$	A	166–168	14	EtOH	$C_{21}H_{29}Cl_2N_7$	C, H, N
52	3,4-Cl_2		C	164–170	32	MeCN	$C_{18}H_{23}Cl_2N_7$	C, H, N
53	3,4-Cl_2		C	210–212	48	EtOH	$C_{19}H_{19}Cl_2N_7$	C, H, N
54	3,4-Cl_2		A	188–190	15	EtOH	$C_{19}H_{25}Cl_2N_7$	C, H, N
55	3,4-Cl_2		C	214–215	40	EtOH–H_2O	$C_{19}H_{25}Cl_2N_7$	C, H, N

Table I (*Continued*)

No.	X, Y, Z	NRANR$_1$R$_2$	Procedure	Mp, °C	Yield, purified, %	Purificn solvent	Formula	Analyses
56	3,4-Cl_2		C	154–157	10	MeCN	$C_{19}H_{25}Cl_2N_7$	C, H, N
57	3,4-Cl_2		C	181–183	49	MeCN	$C_{20}H_{27}Cl_2N_7$	C, H, N
58	3,4-Cl_2		C	176	5	MeCN	$C_{21}H_{29}Cl_2N_7$	C, H, N
59	3,4-Cl_2		C	189–192	25	MeCN	$C_{18}H_{23}Cl_2N_7$	C, H, N
60	3,4-Cl_2		C	115–159 indef	7	MeCN	$C_{18}H_{23}Cl_2N_7$	C, H, N
61	3,4-Cl_2		B	153–154	15	MeCN	$C_{19}H_{25}Cl_2N_7$	C, H, N
62	3,4-Cl_2		C	132–135	11	MeCN	$C_{20}H_{27}Cl_2N_7$	C, H, N
63	3,4-Cl_2		C	178–184	2	MeCN	$C_{20}H_{27}Cl_2N_7 \cdot 0.5HCl$	C, H, N, Cl
64	3,4-Cl_2		C	99–102	4	*n*-Heptane	$C_{20}H_{27}Cl_2N_7 \cdot 0.44H_2O$	C, H, N, H_2O
65	3,4-Cl_2		C	114–119	3	*n*-Heptane	$C_{21}H_{29}Cl_2N_7$	C, H, N
66	3,4-Cl_2		C	170–172	7	MeCN	$C_{21}H_{29}Cl_2N_7$	C, H, N
67	3,4-Cl_2		C	191–193	9	MeCN	$C_{24}H_{27}Cl_2N_7$	C, H, N
68	3,4-Cl_2		A	205–207	43	EtOH	$C_{22}H_{25}Cl_2N_7O$	C, H, N
69	3,4-Cl_2		A	213–214	17	EtOH	$C_{23}H_{27}Cl_2N_7O$	C, H, N
70	3,4-Cl_2		A	205–208	17	MeOH–H_2O	$C_{24}H_{29}Cl_2N_7O$	C, H, N
71	3,4-Cl_2		A	214–215	35	DMF–H_2O	$C_{24}H_{29}Cl_2N_7O$	C, H, N

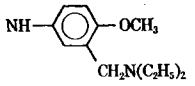
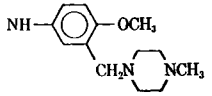
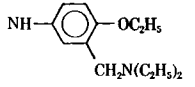
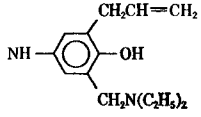
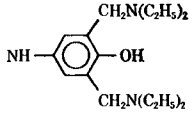
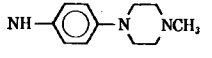
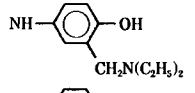
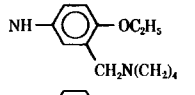
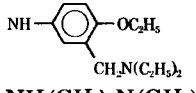
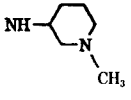
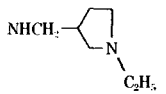
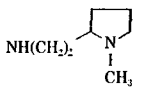
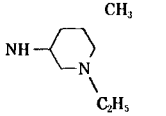
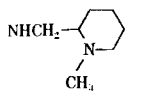
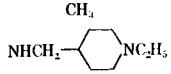
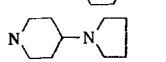
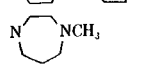
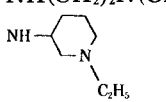
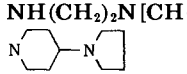
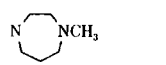
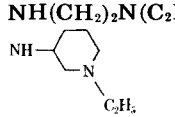
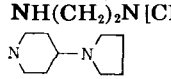
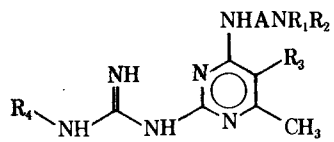
72	3,4-Cl_2		A	220–223	47	MeCN	$C_{24}H_{29}Cl_2N_7O$	C, H, N
73	3,4-Cl_2		A	213	14	MeCN	$C_{25}H_{30}Cl_2N_8O$	C, H, N
74	3,4-Cl_2		A	185–187	44	EtOH–H_2O	$C_{25}H_{31}Cl_2N_7O$	C, H, N
75	3,4-Cl_2		A	154–157	4	MeCN	$C_{26}H_{31}Cl_2N_7O$	C; H, N[g]
76	3,4-Cl_2		A	151–153	24	MeCN	$C_{28}H_{38}Cl_2N_8O$	C, H, N
77	3,4-Cl_2	$N(CH_3)_2$	D	175–177	12	MeCN	$C_{14}H_{16}Cl_2N_6$	C, H, N
78	3,4-Cl_2	$N(C_2H_5)_2$	E	247–249	10	MeCN	$C_{16}H_{20}Cl_2N_6 \cdot HCl$	C, H, N
79	3,4-Cl_2	1-NH-4-$O(CH_2)_2OHC_6H_4$	A	213–216	21	MeCN	$C_{20}H_{20}Cl_2N_6O_2$	C, H, N
80	3,4-Cl_2		A	285–287	58		$C_{23}H_{26}Cl_3N_8 \cdot 2HCl \cdot 0.5H_2O$	C, H, N, Cl, H_2O
81	3,4-Cl_2	1-NH-3-$CH_2N(C_2H_5)_2C_6H_4$	A	149.5–150	66	MeCN	$C_{23}H_{27}Cl_2N_7$	C, H, N
82	3,4-Cl_2	1-NH-4-$CH_2N(C_2H_5)_2C_6H_4$	A	169–170	49	*i*-PrOH	$C_{23}H_{27}Cl_2N_7$	C, H, N
83	3,5-Cl_2	$NH(CH_2)_2N(C_2H_5)_2$	A	160–161[n]	54	EtOH–H_2O	$C_{18}H_{25}Cl_2N_7$	C, H, N
84	3,5-Cl_2	$NH(CH_2)_2N(CH_2CH{=}CH_2)_2$	C	172–174	15	MeCN	$C_{20}H_{25}Cl_2N_7$	C, H, N
85	3,5-Cl_2	$NH(CH_2)_2N[CH(CH_3)_2]_2$	C	155–157	55	MeCN	$C_{20}H_{29}Cl_2N_7$	C, H, N
86	3,5-Cl_2	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	C	178–180 dec	16	*i*-PrOH–C_6H_{12}	$C_{21}H_{31}Cl_2N_7 \cdot 2HCl \cdot 1.3H_2O$	C, N, Cl; H, H_2O[k]
87	3,5-Cl_2	NH-3-$N(C_2H_5)_2C_6H_{10}$	C	103–115	11	Isooctane	$C_{22}H_{31}Cl_2N_7$	C, H; N[i]
88	3,5-Cl_2	1-NH-4-$N(C_2H_5)_2C_6H_{10}$	C	202.5–205	4		$C_{22}H_{31}Cl_2N_7 \cdot HCl$	C, H, N
89	3,5-Cl_2		A	199–201	30	EtOH–*i*-PrOH	$C_{23}H_{27}Cl_2N_7O$	C, H, N
90	3,5-Cl_2		A	226–228	47	EtOH–MeOH	$C_{25}H_{29}Cl_2N_7O$	C, H, N
91	3,5-Cl_2		A	190–192	51	*i*-PrOH	$C_{25}H_{31}Cl_2N_7O$	C, H, N
92	3,5-Cl_2	$NH(CH_2)_2N(CH_2)_4$	C	191–193	35	MeCN	$C_{18}H_{23}Cl_2N_7$	C, H; N[i]
93	3,5-Cl_2		C	212–214	18	MeCN	$C_{18}H_{23}Cl_2N_7$	C, H, N
94	3,5-Cl_2	$NH(CH_2)_3N(CH_2)_4$	C	157–159	17	MeCN	$C_{19}H_{25}Cl_2N_7$	C, H, N

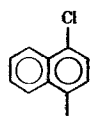
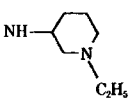
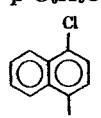
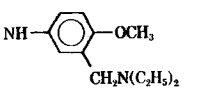
Table I (*Continued*)

No.	X, Y, Z	NRANR$_1$R$_2$	Procedure	Mp, °C	Yield, purified, %	Purifcn solvent	Formula	Analyses
95	3,5-Cl_2		C	201–203	40	MeCN	$C_{19}H_{25}Cl_2N_7$	C, H, N
96	3,5-Cl_2		C	198–199	51	MeCN	$C_{19}H_{25}Cl_2N_7$	C, H, N
97	3,5-Cl_2		C	155–160	30	MeCN	$C_{19}H_{25}Cl_2N_7$	C, H, N
98	3,5-Cl_2		C	174–176	29	MeCN–*i*-PrOH	$C_{19}H_{25}Cl_2N_7$	C, H, N
99	3,5-Cl_2		C	178–180	14	C_6H_6–MeCN	$C_{20}H_{27}Cl_2N_7 \cdot 0.2H_2O \cdot 0.1C_6H_6$	H, Cl; C, N, H_2O[k]
100	3,5-Cl_2		A	272–274 dec	44	MeOH	$C_{21}H_{27}Cl_2N_7 \cdot 2HCl \cdot 2.7H_2O$	C, N, H_2O; H[l]
101	3-CF_3, 4-Br		C	172–174	21	MeCN	$C_{19}H_{23}BrF_3N_7$	C, H, N
102	3-CF_3, 4-Br	$NH(CH_2)_2N(C_2H_5)_2$	C	141–143	39	MeCN	$C_{19}H_{25}BrF_3N_7$	C, H, N
103	3-CF_3, 4-Br	$NH(CH_2)_2N(CH_2)_5$	C	140–143	60	MeCN	$C_{20}H_{25}BrF_3N_7$	C, H, N
104	3-CF_3, 4-Br		C	150–151	11	C_6H_{12}	$C_{20}H_{25}BrF_3N_7$	C, H, N
105	3-CF_3, 4-Br	$NH(CH_2)_2N(CH_2)_6$	C	167–169	52	MeCN	$C_{21}H_{27}BrF_3N_7$	C, H, N
106	3-CF_3, 4-Br	$NH(CH_2)_2N(C_2H_5)(CH_2)_3CH_3$	C	90–93	46	MeCN	$C_{21}H_{29}BrF_3N_7$	C, H, N
107	3-CF_3, 4-Br	$NH(CH_2)_2N[CH(CH_3)_2]_2$	C	173–175	70	MeCN	$C_{21}H_{29}BrF_3N_7$	C, H, N
108	3-CF_3, 4-Br		A	161–162	11	MeCN	$C_{22}H_{27}BrF_3N_7$	C, H, N
109	3-CF_3, 4-Cl		C	170–173.5	17	EtOAc	$C_{19}H_{23}ClF_3N_7 \cdot 0.5HCl \cdot 0.67H_2O$	C, H, N, Cl^-, H_2O
110	3-CF_3, 4-Cl	$NH(CH_2)_2N(C_2H_5)_2$	C	137–138	77	MeCN	$C_{19}H_{23}ClF_3N_7$	C, H, N
111	3-CF_3, 4-Cl		C	132–135.5	26	C_6H_{12}	$C_{20}H_{25}ClF_3N_7$	C, H, N
112	3-CF_3, 4-Cl	$NH(CH_2)_2N(CH_2)_6$	C	160–162	64	*n*-C_7H_{16}	$C_{21}H_{27}ClF_3N_7$	C, H, N
113	3-CF_3, 4-Cl	$NH(CH_2)_2N[CH(CH_3)_2]_2$	C	175–178	70	MeCN	$C_{21}H_{29}ClF_3N_7$	C, H, N
114	3-CF_3, 4-Cl		C	162–164	35	MeCN	$C_{22}H_{27}ClF_3N_7$	C, H, N

[a]N: calcd, 21.02; found, 20.57. [b]H: calcd, 5.78; found, 5.09. [c]H_2O: calcd, 3.55; found, 4.09. [d]H: calcd, 5.63; found, 5.21. [e]N: calcd, 18.26; found, 17.80; Cl: calcd, 13.21; found, 12.80; H_2O: calcd, 2.86; found, 2.43. [f]C: calcd, 44.83; found, 44.26. [g]H: calcd, 5.42; found, 5.83; N: calcd, 18.55; found, 18.08. [h]H: calcd, 6.53; found, 6.08; H_2O: calcd, 4.27; found, 4.89. [i]N: calcd, 21.11; found, 20.47. [j]N: calcd, 24.01; found, 23.55. [k]C: calcd, 55.25; found, 54.81; N: calcd, 21.90; found, 21.45; H_2O: calcd, 0.81; found, 0.33. [l]H: calcd, 6.08; found, 5.49. [m]Lit.[4] reports mp 154–155°. [n]Lit.[17] reports mp 158–159°.

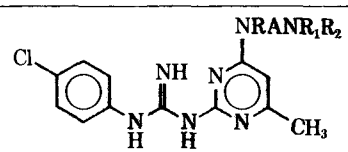
Table II. Other 1-Substituted 3-[4-[[(Dialkylamino)alkyl]amino]-2-substituted pyrimidinyl]guanidines



No.	R_4	$NHANR_1R_2$	R_3	Procedure	Mp, °C	Yield purified, %	Purificn solvent	Formula	Analyses
115	3,4-$Cl_2C_6H_3$–	$NH(CH_2)_2N(C_2H_5)_2$	CH_3	C	106–111	6	MeCN	$C_{19}H_{27}Cl_2N_7$	C, H, N
116	3,4-$(CH_3O)_2C_6H_3$–	$NH(CH_2)_2N(C_2H_5)_2$	H	A	183–185	22	MeCN	$C_{20}H_{31}N_7O_2$	C, N; H[a]
117	3,4-$Cl_2C_6H_3CH_2$–	$NH(CH_2)_2N[CH(CH_3)_2]_2$	H	C	86–89	18		$C_{21}H_{31}Cl_2N_7 \cdot 0.5HCl$	C, H, N, Cl, Cl⁻
118	3,4,5-$(CH_3O)_3C_6H_2$–	$NH(CH_2)_2N(C_2H_5)_2$	H	C	168–169	23	MeCN	$C_{21}H_{33}N_7O_3$	C, H; N[b]
119	*p*-$CH_3(CH_2)_3C_6H_4$–	$NH(CH_2)_2N(C_2H_5)_2$	H	A	115–116 (130–131)	28	MeCN	$C_{22}H_{35}N_7$	C, H, N
120			H	C	173–176	19	MeCN	$C_{23}H_{28}ClN_7$	C, H, N
121	3,4-$Cl_2C_6H_3$–	$NH(CH_2)_2N(C_2H_5)_2$	$CH_2C_6H_5$	C	124–125	14	MeCN	$C_{25}H_{31}Cl_2N_7$	C, H, N
122	*p*-$C_6H_5CH_2OC_6H_4$–	$NH(CH_2)_2N(C_2H_5)_2$	H	A	151–153	29	MeCN	$C_{25}H_{33}N_7O$	C, H, N
123			H	C	212–214	24	EtOH–MeOH (9:1)	$C_{28}H_{32}ClN_7O$	C, H, N

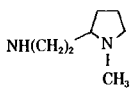
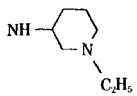
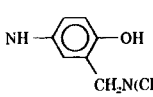
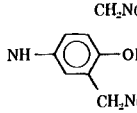
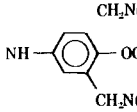
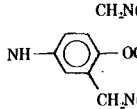
[a]H: calcd, 7.76; found, 7.30. [b]N: calcd, 22.72; found, 23.21.

Table III. Effects of 1-(*p*-Chlorophenyl)-3-[4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



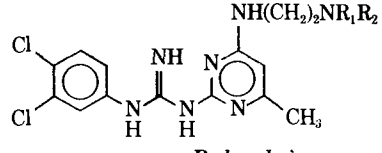
		P. berghei									*P. gallinaceum* single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[c] after mg/kg							
No.	$NRANR_1R_2$	No. of mice	SD_{90},[a] mg/kg/day	*Q*[b]	640	320	160	80	40	20	mg/kg	ΔMST, T or C[d]
1	$N[(CH_2)_2]_2NCH_3$	21	42	1.8	12.7 11.8	8.2	3.9 4.0	0.6	0.3 0.2	0.2	120	0.9
2	$NH(CH_2)_2N(C_2H_5)_2$	21	68	1.1	T5		T5 7.9, T3	7.9, T2	6.3 6.9	2.7	100	12.3, C4
3	$NH(CH_2)_3N(CH_2)_4$				C1, T2	C1, T2	7.1	4.1	3.9	0.7	240 120 60	12.7, C1 14.6 8.6

Table III (*Continued*)

No.	NRANR$_1$R$_2$	*P. berghei* Diet, 6 days: No. of mice	SD_{90},[a] mg/kg/day	Q[b]	*P. berghei* Single sc dose; ΔMST, T or C[c] after mg/kg: 640	320	160	80	40	20	*P. gallinaceum* single sc dose: mg/kg	ΔMST, T or C[d]
4		7	>142	<0.5	7.7, C1 6.9, C2	6.4, C1	4.9 3.5	0.9	0.7 0.1	0.5	120 60	19.7, C1 15.6
5		21	83	0.9	C5 C5	22.9, C4	13.9, C4 9.9, C3	8.4, C1	8.1 3.5	1.1		
6	1-NH-4N$(CH_3)_2C_6H_{10}$	7	>215	<0.3	8.2 7.5	4.5 4.0	1.6 1.4	1.3 1.0	0.9 0.7	0.5 0.2	120	2.3
7	$NH(CH_2)_2N[CH(CH_3)_2]_2$	21	45	1.7	13.9, C4 15.9, C3	14.9, C1	9.9 6.9	4.3	3.7 2.3	0.9	120	19.3, C1
8	$NH(CH_2)_3N(CH_2)_6$				C2, T3	7.5, T3	7.0, T3	6.5, T2	4.7	3.5	240 120 60	12.3, C3 12.5, C2 12.5, C2
10		21	42	1.8	7.4 7.4	5.2	2.0 1.6	0.8	1.0 0.8	0.4		
11		14	110	0.7	8.3, C1 10.5	7.4	6.8 5.1	2.8	2.1 2.0	0.4		
12		7	>139	<0.5	5.4	4.0	3.2 1.8	2.0	0.8 0.2	0.6		
13		7	>148	<0.5	C1, T4 C1, T4	9.7	5.5 4.9	4.5	2.3 0.9	0.7	120	14.1, C2
	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 hydrochloride (74.5 mg of 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 postinfection and termed "cured;" data to establish parasitological cure based on subinoculation 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 postinfection and termed "cured;" data to establish parasitological cure based on subinoculation are unavailable. T indicates the number of deaths occurring within 48 hr after infection which are attributed to drug action and are counted as toxic deaths. Control birds do not die before 48 hr. Each entry at each dose level represents results with a five-animal group. [e] Tested parenterally as the sulfate and by diet as the hydrochloride.

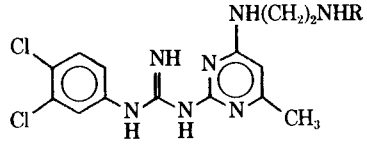
Table IV. Effects of 1-(3,4-Dichlorophenyl)-3-[4-[[(dialkylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



		P. berghei								*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg						
No.	NR_1R_2	No. of mice	SD_{90},[a] mg/kg/day	Q[a]	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
14	$N(C_2H_5)_2$	21	17	4.2	C3, T2	C5	C5	C5	7.9, C3	7.3	120	18.4, C3
					C3, T2		C5		8.7		60	16.4, C1
											30	12.0
15	$N(CH_3)(CH_2)_3CH_3$	21	11	6.8	C3, T2	C4, T1	C5	15.6, C3	8.6, C2	6.2	120	7.4
					C4, T1		C5		7.7, C1			
16	$N(CH_2CH{=}CH_2)_2$	21	40	1.9	C5	C5	C5	10.1, C1	7.4	4.8		
					C5	C5	C5					
17	$N(C_2H_5)(CH_2)_3CH_3$	28	10	7.5	C4, T1	C5	C5	15.5, C3	9.5, C2	5.1	120	8.0, C1
					C3, T2		C5		12.6, C1			
18	$N[CH(CH_3)_2]_2$	21	24	3.1	C5	C5	C5	15.5, C3	14.0, C1	3.3, C1	120	8.5, C1
					C5		28.6, C4		13.9, C1			
19	$N[(CH_2)_3CH_3]_2$	14	29	2.6	C5	C5	25.5, C3	8.5, C2	8.9	2.7	120	6.4
					C5		21.6, C4		8.8		60	5.6
											30	3.6
20	$N[CH(CH_3)C_2H_5]_2$	21	38	2.0	C5	C5	8.6, C4	12.0	6.4	2.2	120	0.1
					C5		18.1, C3		5.8			

[a]See footnotes *a–d*, Table III.

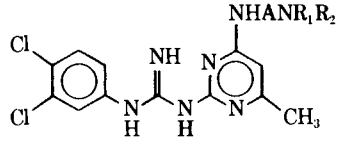
Table V. Effects of 1-(3,4-Dichlorophenyl)-3-[4-[[(monoalkylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

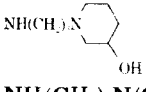


		P. berghei									*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	NHR	No. of mice	SD_{90},[a] mg/kg/day	Q^a	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
21	NHC_2H_5[b]				1.0		0.2		0.2		320	0.2
22	$NHCH_2CH{=}CH_2$				T5	T5	C3, T2	C3, T1	14.4, C3	5.1	100	5.6
							C3, T2		13.4, C3			
23	$NHCH(CH_3)_2$[b]				21.2, C1	9.5	4.9	2.5	0.6	0.1	120	0.6
					16.1, C2		4.8		0.3			
24	$NHCH_2CHOHCH_3$	7	>35	<2.1	10.8, C2	7.5, C2	3.7	2.9	1.9	1.5	120	0.4
					10.3, C2		3.8		1.6			
25	$NHCH(CH_3)C_2H_5$				T5	C2, T3	C3, T2	C3, T1	8.9, C2	3.7	120	7.4, C1
					C1, T4		C3, T1		6.8, C2		60	6.1, C1
26	$NHCH_2COH(CH_3)_2$	7	>37	<2.0	C2, T3	C2, T3	9.2, C1	7.9	3.7	2.1	100	2.0
					C1, T3		8.4, C1		3.3			

[a]See footnotes *a–d*, Table III. [b]Tested as the HCl salt.

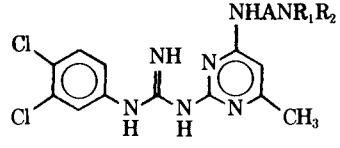
Table VI. Effects of 1-(3,4-Dichlorophenyl)-3-[4-[[(hydroxyalkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



		P. berghei									*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	$NHANR_1R_2$	No. of mice	SD_{90},[a] mg/kg/day	Q^a	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
27	$NH(CH_2)_2N(C_2H_5)(CH_2)_2OH$	7	>36	<2.1	C2, T3	C3, T1	9.9	2.3	1.1	0.3	100	2.0
					C2, T3		10.1		0.9			
28	$NHCH_2CHOHCH_2N(C_2H_5)_2$[b]	7	>36	<2.1	C2, T3	C3, T2	9.9, C3	8.7, C1	8.1	5.3	120	2.0
					C2, T3		8.9, C2		7.7			
29		7	>33	<2.3	T5	T5	4.9, T2	3.9	2.7	1.7	100	1.0
							4.4, T1		2.3			
30	$NH(CH_2)_2N(C_2H_5)CH_2COH(CH_3)_2$	21	41	1.8	C5	21.3, C3	8.8, C1	7.6	3.2	3.0	120	16.7, C1
					C5	12.8, C4	7.8, C1					

[a]See footnotes *a–d*, Table III. [b]Tested as the HCl salt.

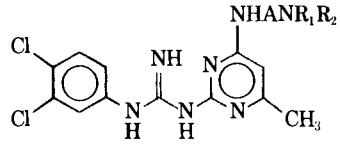
Table VII. Effects of Side-Chain Branched 1-(3,4-Dichlorophenyl)-3-[4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

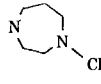
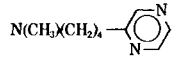
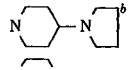
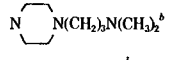
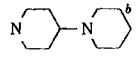


		P. berghei									*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	$NHANR_1R_2$	No. of mice	SD_{90},[a] mg/kg/day	Q^a	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
31	$NHCH(CH_3)CH_2N(CH_3)_2$	21	23	3.2	C2, T3 C2, T3	C4, T1 C4, T1	C5 C5	11.8, C3	8.0	4.6	100	13.9
32	$NHCH_2CH(CH_3)N(CH_3)_2$	28	10	7.5	C2, T1 C1, T3	25.9, C4	21.9, C4 13.9, C4	23.9, C2	12.5 11.7	8.5		
33	$NHCH(CH_3)CH_2N(C_2H_5)_2$	14	31	2.4	C5	C5 C5	C5 C5	22.8, C4	14.9, C1 14.1, C1 15.4, C1	8.2[b] 8.7 8.9	320 160 80	5.6, T3 5.8 5.4
34	$NHCH_2CH(CH_3)N(C_2H_5)_2$	14	15	4.8	C4, T1 C2, T3	C4, T1	C5 C5	C5	10.9, C3 9.2, C2	4.7	120	8.4
35	1-NH-4-$N(CH_3)_2C_6H_{10}$					8.2 6.6	4.0	3.6 0.8	2.6	0.4 0.2		
36	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	7	>18	<4.1	C2, T3 C3, T2	C3, T2	C2, T1 C2, T1	12.1, C2	5.8 5.2	2.6	120	5.2
37	$NHCH_2C(CH_3)_2CH_2N(C_2H_5)_2$[c]	21	11	6.8	C5 C5	C5	17.5, C3 9.6, C4	4.9	3.3 3.2	1.3	120	0.4
38	$NHCH(CH_3)CH_2N(CH_2CH_2CH_3)_2$[c]	14	2.5	30		C5	C5 C5	16.8, C3 14.8, C3	7.8 7.4	0.8 0.6	320 160 80	9.1 7.3 3.3
39	1-NH-4-$N(C_2H_5)_2C_6H_{10}$	7	>17	<4.4	T5	C2, T2	8.9, C1 7.4, C1	8.5	5.1 5.3	3.1	120	3.0, T2

[a] See footnotes *a–d*, Table III. [b] ΔMST 6.5 days at 10 mg/kg. [c] Tested as the HCl salt.

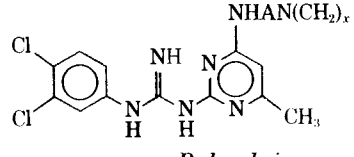
Table VIII. Effects of 1-(3,4-Dichlorophenyl)-3-[4-[[(dialkylamino)alkyl]alkylamino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



		P. berghei									*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	$NRANR_1R_2$	No. of mice	SD_{90},[a] mg/kg/day	Q[a]	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
40		21	38	2.0	C5 C5	19.8, C4 25.3, C3	17.8, C2 17.8, C3	11.6, C1	4.6	1.2		
41	$N(CH_3)CH_2CH(CH_3)N(CH_3)_2$[b]				6.8 6.5	4.8	2.8 2.7	0.4	0.2 0.1	0.2	120	0.7
42	$N(CH_3)(CH_2)_2N(C_2H_5)_2$[b]	14	7	11	T5	C5	C5 C5	9.7, C3	8.5 8.4	0.5	100	1.3
43		14	110	0.7	9.1 9.0		5.7 5.4		3.7 3.6			
44		28	8	8.8	C2, T3 C3, T2	C5 C3, T2	29.8, C4 C5	21.8, C4	8.4	1.4	120	1.2
45					T5 T5		T5 T5		1.9 2.1			
46					C2, T3 C3, T2	28.9, C3	28.4 27.7	16.9	9.0 9.5	1.3	120	5.6

[a]See footnotes *a–d*, Table III. [b]Tested as the HCl salt.

Table IX. Effects of 1-(3,4-Dichlorophenyl)-3-[4-[[(heterocyclic)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

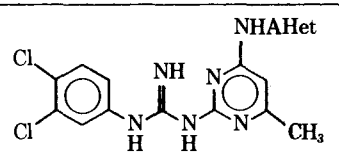


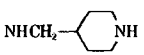
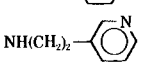
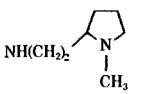
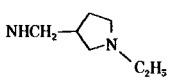
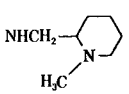
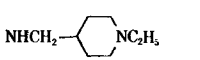
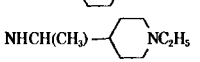
		P. berghei									*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	$NHAN(CH_2)_x$	No. of mice	SD_{90},[a] mg/kg/day	Q[a]	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
47	$NH(CH_2)_2N(CH_2)_1$	21	31	2.4	T5	C4, T1	C5 C5	15.1, C3	13.2, C1 13.6, C1	6.6	100	5.7, C1

48	$NH(CH_2)_3N(CH_2)_4$	14	77	1.0	28.3, C3 28.9, C3	18.7, C1 17.0, C2	6.0 6.7, C1 8.1, C1	7.2 5.4, C1	3.0 3.7 3.8	3.1 2.8	120	19.2, C2
49	$NH(CH_2)_2N(CH_2)_5$	14	15	4.8	C5 C5	C5	C5 C5	22.9, C4	9.9, C3 17.2, C2	6.5	120	7.8
50	$NH(CH_2)_2N(CH_2)_6$	14	14	5.1	C5 C5	C5	18.0, C3 9.6, C4	12.2, C2	6.5, C2 6.4, C1	3.9	120 60 30	8.4 7.6 6.6
51	$NH(CH_2)_3N(CH_2)_6$	21	42	1.8	C3, T1 C3, T2	C2, T2 C3, T1	12.3, C1 11.4, C1 8.5, C2	8.9, C1 7.3, C1	3.8 4.9 4.2	3.5 4.0	120	14.5, C1

[a]See footnotes *a–d*, Table III.

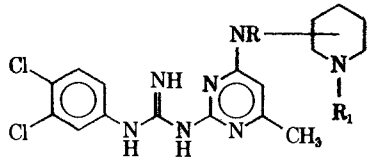
Table X. Effects of Branched 1-(3,4-Dichlorophenyl)-3-[4-[[(heterocyclic)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



		P. berghei									*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	NHAHet	No. of mice	SD_{90},[a] mg/kg/day	Q^a	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
52		7	>33	<2.2	T5		1.8, T3		1.2		120	0.9
53		14	98	0.8	8.4 7.9	5.6	3.0 2.9	1.4	0.8 0.7	0.6	100	0.2
54		21	46	1.6	9.3, Cl 10.2, C2	9.2, C2 10.5, C2	8.3, C1 9.4, C1 8.3, C1	8.3 8.4	5.2 5.7 6.0	4.7 3.4	120	13.2, C1
55		7	>15	<5.0	C3, T2 C4, T1	C5	C2, T1 11.7, C2	8.5, C1	5.2 5.5	2.1	120	4.3
56											320 160 80 40 20	9.8, T2 6.1, T1 5.3 3.7 2.5
57		7	>21	<3.5	C3, T2 C3, T2	C2, T1	11.2, C2 10.9, C2	4.7	1.3 1.3	0.7	100	2.1
58					C3, T2	C3, T2 C3, T1	18.3, C1 13.8, C2	6.4 6.6	3.8 4.0	3.0 2.8		

[a]See footnotes *a–d*, Table III.

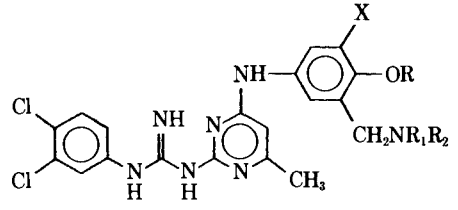
Table XI. Effects of 1-(3,4-Dichlorophenyl)-3-[4-methyl-6-[(1-alkyl-3- or -4-piperidyl)amino]-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



No.	NR–(N)–R_1	Diet, 6 days: No. of mice	Diet, 6 days: SD_{90},[a] mg/kg/day	Diet, 6 days: Q^a	*P. berghei*: Single sc dose; ΔMST, T or C[a] after mg/kg: 640	320	160	80	40	20	*P. gallinaceum*, single sc dose: mg/kg	*P. gallinaceum*, single sc dose: ΔMST, T or C[a]
59	NH–(N)–CH_3	14	17	4.3	C5 C5	C5	24.9, C4 21.9, C4	14.4, C3	7.7, C1 7.2, C1	5.5	100	6.4
60	NH–(N)–NCH_3				T5	C3, T2	C1, T3 C2, T2	16.0, C2	C1, T1 11.5, C1	5.5	100	3.1
61	NH–(N)–C_2H_5	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
62	NH–(N)–$CH_2CH_2CH_3$	14	17	4.4	C5 C5	C5	C5 C5	C5	C5 C5 C10 31.8, C9	2.7 2.8 2.7	100	7.3
63	NH–(N)–$NCH_2CH_2CH_3$[c]	14	17	4.4	C5	C5 C5	C5 C5	C5 C5	C5 C5	7.8, C3[b] 9.3, C3	120	6.7
64	$N(CH_3)$–(N)–C_2H_5					C5	C5 C5	21.7, C4 25.8, C4	13.1 13.0	4.5 4.8	120 30	4.8 2.0
65	NH–(N)–$CH_2CH(CH_3)_2$					C5	C5 C5	17.4, C3 17.9, C3	9.1 8.9	3.9 3.9		
66	NH–(N)–$NCH_2CH(CH_3)_2$				C5	C5 C5	C5 C5	C5 C5	22.9, C3 23.9, C3	13.9 14.1		
67	NH–(N)–$NCH_2C_6H_5$				18.5, C2 16.8, C2	9.6	7.6 7.6	5.6	1.2 0.8	0.8	120	6.7

[a]See Footnotes *a–d*, Table III. [b]ΔMST 3.0 days at 10 mg/kg. [c]Tested as the HCl salt.

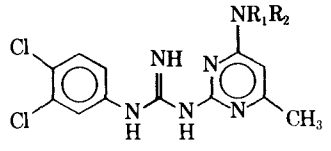
Table XII. Effects of 1-(3,4-Dichlorophenyl)-3-[4-[α-(mono- and dialkylamino)-4-hydroxy- and alkoxy-*m*-toluidino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

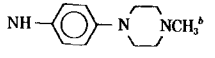


				P. berghei								*P. gallinaceum*, single sc dose	
				Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg						
No.	R	NR_1R_2	X	No. of mice	SD_{90},[a] mg/kg/day	Q^a	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
68	CH_3	NHC_2H_5	H	7	>77	<1.0	5.2 5.0	2.4	1.2 1.0	0.2	0.2 0.4	0.0	120	1.6
69	H	$N(C_2H_5)_2$	H	28	11	7.1	12.8, C3 14.6, C2	10.2	6.2 6.9	4.8	2.2 3.1	0.8		
70	CH_3	$NHCH_2CH(CH_3)_2$	H	14	78	1.0		10.3		3.1 3.9	2.9	0.5 0.9	320 160	0.3 0.3
71	CH_3	$N(C_2H_5)_2$	H	21	53	1.4	10.4 10.1	8.6	7.8 8.3	4.4	2.8 3.3	0.4		
72	CH_3	$N(CH_3)CH(CH_3)_2$	H	21	24	3.1	23.2, C2 19.8, C3	12.2, C1	9.7 9.2	8.5	1.9 1.2	0.9	120	4.0
73	CH_3		H				5.7	5.3	0.3 1.1	0.9	0.3 0.9	0.5	100	1.7
74	C_2H_5	$N(C_2H_5)_2$	H	21	42	1.8	9.4 8.3	8.2	6.4 4.2	5.6	4.2 3.8	1.6	100	9.1
75	H	$N(C_2H_5)_2$	$CH_2CH{=}CH_2$				14.3, C3		11.4	6.9	2.0 2.3	2.1	120	0.0
76	H	$N(C_2H_5)_2$	$CH_2N(C_2H_5)_2$	7	>33	<2.3	10.8, C2 16.1, C1	11.5	7.1 6.6	5.5	3.7 3.2	3.3	120 60	0.4 0.4

[a]See footnotes *a–d*, Table III.

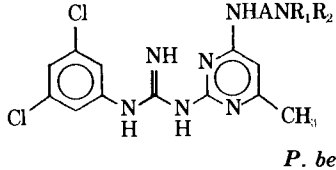
Table XIII. Effects of Miscellaneous 1-(3,4-Dichlorophenyl)-3-(4-amino-6-methyl-2-pyrimidinyl)guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



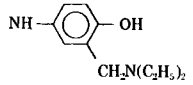
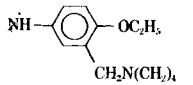
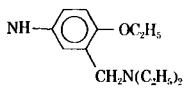
		P. berghei								*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	NR_1R_2	No. of mice	SD_{90},[a] mg/kg/day	Q[a]	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
77	$N(CH_3)_2$				5.1	2.9	2.1	0.7	0.3	0.3	120	0.0
					4.9		1.9		0.3			
78	$N(C_2H_5)_2$[b]				8.2, T1	6.9	6.3	0.5	0.3	0.3	120	1.7
					7.8, T1		6.2		0.4			
79	1-NH-4-$O(CH_2)_2OHC_6H_4$	7	>169	<0.4	2.1		0.9		0.3			
80		14	65	1.1	1.8		1.2		0.2			
81	1-NH-3-$CH_2N(C_2H_5)_2C_6H_4$	14	95	0.8	16.1, C2	12.6	6.0	4.6	1.8	0.6		
					7.3, C3		13.0		5.6			
82	1-NH-4-$CH_2N(C_2H_5)_2C_6H_4$	21	42	1.8	14.6	10.0	7.8	7.0	4.0	0.8	100	4.8
					14.8		10.6		8.2			

[a]See footnotes *a–d*, Table III. [b]Tested as the HCl salt.

Table XIV. Effects of 1-(3,5-Dichlorophenyl)-3-[4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines and 1-(3,5-Dichlorophenyl)-3-[4-[α-(dialkylamino)-4-hydroxy- and alkoxy-*m*-toluidino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

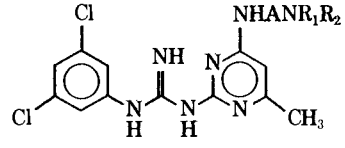


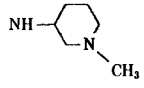
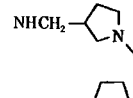
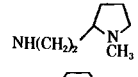
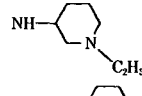
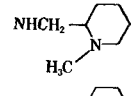
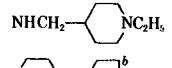
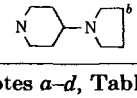
		P. berghei									*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	$NHANR_1R_2$	No. of mice	SD_{90},[a] mg/kg/day	Q[a]	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
83	$NH(CH_2)_2N(C_2H_5)_2$	28	10	7.5	C5	26.9, C4	22.9, C4	13.9, C4	10.5	6.1	100	19.3
84	$NH(CH_2)_2N(CH_2CH{=}CH_2)_2$	14	15	4.8	C5	27.9, C4	23.9, C4	11.9	8.7	4.3	100	0.8
					C5		26.4, C3		8.5			
85	$NH(CH_2)_2N[CH(CH_3)_2]_2$	21	26	2.9	C5	C5	19.6, C4	14.4, C1	8.4	1.8	120	6.4
					C5		24.7, C3		8.1			
86	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$[b]	14	63	1.2	T5	C2, T1	C2, T1	12.4	6.8	5.6	120	4.2
							C2, T2		6.2			
87	1-NH-3-$N(C_2H_5)_2C_6H_{10}$					C2, T3	C2, T1	9.3, C1	6.4	4.2	160	5.1, T2
						C1, T3		9.6, C1		3.8	80	4.1
											40	2.7
88	1-NH-4-$N(C_2H_5)_2C_6H_{10}$[b]				C2, T3	C3, T2	15.3, C3	9.8, C3	11.8	0.8	120	4.1
					C3, T2		14.7, C3		10.9		60	2.3

89		14	30	2.5	C5 C5	22.7, C4	11.7, C2 10.8, C2	7.5	5.9 5.8	2.5	120	2.5
90		14	30	2.5	22.5, C2 18.2, C3	10.6	8.8 8.5	4.6	2.2 1.7	0.6	240 120	2.7 0.3
91		14	18	4.1	10.8, C3 9.2, C3	14.6	10.8 10.3	8.4	5.2 4.7	3.8	120 60	4.3 2.7

[a]See footnotes *a–d*, Table III. [b]Tested as the HCl salt.

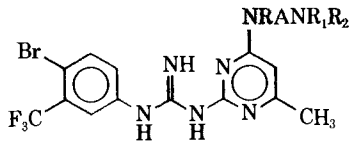
Table XV. Effects of 1-(3,5-Dichlorophenyl)-3-[4-[[(heterocyclic)alkyl]amino- and piperidino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

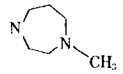
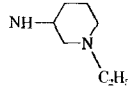
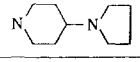


		P. berghei									*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	$NRANR_1R_2$	No. of mice	SD_{90},[a] mg/kg/day	Q[a]	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
92	$NH(CH_2)_2N(CH_2)_4$	14	15	4.8	C5 C5	C5	21.5, C4 25.6, C3	13.5, C3	11.8, C1 12.1, C1	3.1	120 60 30	7.2, C1 6.4 5.8
93		14	16	4.5	C5 C5	C5	12.7, C4 9.3, C3	11.4, C2	10.9 11.4	3.1	120	7.1
94	$NH(CH_2)_3N(CH_2)_4$	7	>21	<3.5	T5	C2, T3	9.9, T2 9.4, T1	7.9, T1	2.1 1.7	0.7		
95		7	>18	<4.1	C5 C4, T1	9.7, C4	18.2, C3 9.8, C4	8.7	6.3 6.2	4.7	120	3.5
96		7	>17	<4.4	16.9, C1 16.7, C1	9.4, C1	11.1 11.7	5.9	4.3 3.9	3.3		
97		14	13	5.5	C5 C5	C5	C5 21.6, C4	9.5, C4	10.2, C2 12.1, C1	10.3	120 60 30	7.0 5.6 5.6
98		21	8.5	8.8	C5 C5	C5	25.3, C3 26.2, C3	9.5, C2	10.6 10.3	4.6	240 120 60	9.7 8.9 8.5
99		7	>39	<1.9	22.8, C3	9.8, C2 10.5, C2	12.4 13.0	11.0 11.4	6.0 6.2	1.8 2.0	120	0.1
100		21	9.5	7.8	C4, T1 C4, T1	C5	C5 30.8, C4	25.8, C2	18.1, C2 17.5, C2	5.4	120	4.6

[a]See footnotes *a–d*, Table III. [b]Tested as the HCl salt.

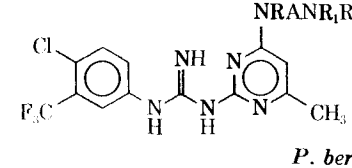
Table XVI. Effects of 1-(4-Bromo-α,α,α-trifluoro-*m*-tolyl)-3-[4-{[(dialkylamino)alkyl]amino}-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

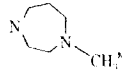


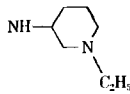
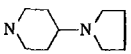
		P. berghei									*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	NRANR$_1$R$_2$	No. of mice	SD$_{90}$,[a] mg/kg/day	Q[a]	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
101		14	17	4.3	C5 C5	C5	27.9, C3 27.9, C4	5.7	0.7 0.5	0.3	120	0.1
102	$NH(CH_2)_2N(C_2H_5)_2$	21	9.2	8.1	C2, T3 C2, T3	C3, T2	C5 C5	C5	9.9, C4 18.9, C3	6.3	100	5.8
103	$NH(CH_2)_2N(CH_2)_5$	14	19	3.9		C5 C5	C5	16.4, C3 20.9, C2	8.5	6.9 6.7	100	6.9
104		21	7.9	9.4	C5 C5	C5	C5 C5	27.9, C4	8.9, C4 8.4, C3	11.9, C1		
105	$NH(CH_2)_2N(CH_2)_6$	14	33	2.2	C5 C5	C5	25.9, C4 21.9, C4	16.4, C3	9.9, C3 9.4, C3	3.9	120	10.7
106	$NH(CH_2)_2N(C_2H_5)(CH_2)_3CH_3$	14	15	5.0	C5 C5	C5	29.9, C4 C5	19.2, C2	10.9, C2 8.9, C2	3.1	320 160 80	12.0, C1 11.3 7.5
107	$NH(CH_2)_2N[CH(CH_3)_2]_2$	14	17	4.4	C5 C5	C5	28.9, C3 27.9, C3	13.2, C1	7.5 7.1	2.3	120	4.5
108						9.9, C4 9.9, C4	16.4, C2	8.9, C2 7.6, C2	3.7	0.7 0.7	320	0.7

[a] See fotnotes *a–d*, Table III.

Table XVII. Effects of 1-(4-Chloro-α,α,α-trichloro-*m*-tolyl)-3-[4-{[(dialkylamino)alkyl]amino}-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks

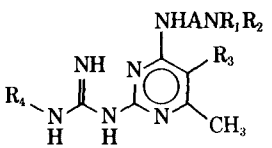


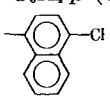
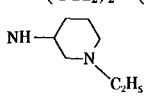
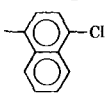
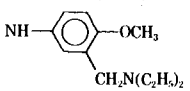
		P. berghei									*P. gallinaceum*, single sc dose	
		Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg							
No.	NRANR$_1$R$_2$	No. of mice	SD$_{90}$,[a] mg/kg/day	Q[a]	640	320	160	80	40	20	mg/kg	ΔMST, T or C[a]
109					C5 C5	25.9, C4	22.9, C4 19.9, C4	6.5	3.5 3.1	0.3		

110	$NH(CH_2)_2N(C_2H_5)_2$	21	7.7	9.7	C1, T4 C2, T3	C4, T1	C5 C5	C5	14.9, C3 18.9, C2	6.7	100	5.0
111		21	19	3.9	C5 C5	C5	C5 8.7, C4	C5	10.9, C3 8.2, C3	8.2, C1		
112	$NH(CH_2)_2N(CH_2)_6$	14	49	1.5	C5 C5	25.9, C4	17.9, C4 24.8, C3	12.1	9.3 8.8	4.5	240 120 60	10.6 6.6 5.8
113	$NH(CH_2)_2N[CH(CH_3)_2]_2$	21	19	3.8	C5 C5	C5	C5 C5	20.3, C3	7.3, C3 8.5, C2	2.8	120	7.8
114		21	18	4.0			C5 C5	15.9, C4	9.5 9.1	3.9	480	0.7

[a]See footnotes *a–d*, Table III. [b]Tested as the HCl salt.

Table XVIII. Effects of Other 1-(Benzyl-, naphthyl-, and phenyl)-3-[4-[[(dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



				P. berghei								*P. gallinaceum*, single sc dose	
				Diet, 6 days			Single sc dose; ΔMST, T or C[a] after mg/kg						
No.	R_4	$NHANR_1R_2$	R_3	No. of mice	SD_{90},[a] mg/kg/day	Q^a	640	320	160	80	40	20	mg/kg	Δ-MST, T or C[a]
115	$-C_6H_3$-3,4-Cl_2	$NH(CH_2)_2N(C_2H_5)_2$	CH_3				C1, T4 T5	13.7, C3	16.0, C2 C3, T1	9.1	4.5 4.2	3.5	100	7.7
116	$-C_6H_3$-3,4-$(OCH_3)_2$	$NH(CH_2)_2N(C_2H_5)_2$	H	7	>130	<0.6	0.6		0.2		0.0			
117	$-CH_2C_6H_3$-3,4-Cl_2	$NH(CH_2)_2N[CH(CH_3)_2]_2$[b]	H	7	>34	<2.2	T5		0.8, T3		0.3, T1		320	0.0
118	$-C_6H_2$-3,4,5-$(OCH_3)_3$	$NH(CH_2)_2N(C_2H_5)_2$	H	7	>197	<0.4	1.3		0.5		0.5			
119	$-C_6H_4$-*p*-$(CH_2)_3CH_3$	$NH(CH_2)_2N(C_2H_5)_2$	H	7	>159	<0.5	1.2	0.8	0.6	0.6	0.4	0.2		
120			H	14	90	0.8	3.9 3.7	1.1	0.9 1.1	0.5	0.5 0.3	0.3	120	0.5
121	$-C_6H_3$-3,4-Cl_2	$NH(CH_2)_2N(C_2H_5)_2$	$CH_2C_6H_5$				3.7, 3.0		2.9, 2.4		1.7, 1.8			
122	$-C_6H_4$-*p*-$OCH_2C_6H_5$	$NH(CH_2)_2N(C_2H_5)_2$	H	7	>104	<0.7	2.9, T3		2.1		0.9			
123			H	7	>84	<0.9	0.4	0.4	0.2	0.2	0.2	0.0	320, 160	0.6, 1.2

[a]See footnotes *a–d*, Table III. [b]Tested as the HCl salt.

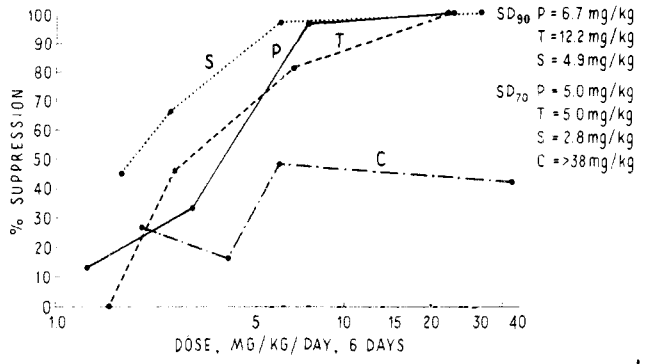


Figure 1. Effects of 1-(3,4-dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine against drug-resistant lines of *P. berghei* in mice.

(11) Saturated heterocyclic side chains are favorable (Tables IX–XI).

(12) A short biospacer between the proximal and distal nitrogen atoms of the side chain is optimal.

(13) The introduction of amodiaquine-type[3] side chains reduces potency, although some derivatives still retain respectable activity (Tables III, XII, XIV).

(14) The linkage of two guanidinopyrimidine moieties *via* a basic piperazine side chain (IX) abolishes activity, although the corresponding chloroquine analog is a potent antimalarial.[3]

Suppressive Antimalarial Effects in Chicks. 1-(*p*-Chlorophenyl)-3-[4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidine (**2**) and 94 related guanidinopyrimidines were also tested for suppressive antimalarial effects against *P. gallinaceum* infections in white Leghorn cockerels (Tables III–XVIII).‡‡,*** 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 maximum 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 among treated chicks that were at least 100% greater than the survival times of untreated control animals.

As a group, the guanidinopyrimidines exhibited strong suppressive antimalarial activity against *P. gallinaceum* in chicks. Fifty-nine compounds increased the mean survival time of chicks >100% at single subcutaneous doses ranging from 30 to 320 mg/kg, and 17 substances (**3, 4, 7, 8, 13, 14, 17, 18, 25, 30, 47, 48, 51, 54, 61, 92,** and **106**) cured chicks at doses of 60–320 mg/kg (Tables III–XVIII). Unfortunately, meaningful structure–activity relationships cannot be deduced utilizing these *P. gallinaceum* test results because inadequate dose–response data are available. However, it is noteworthy that among the new guanidinopyrimidines that were evaluated subcutaneously against both *P. berghei* and *P. gallinaceum*, 56 (75%) of the 75 compounds that exhibited curative activity against *P. berghei* were active against *P. gallinaceum*, while only 2 (12%) of the 17 substances that lacked curative activity against *P. berghei* were active against *P. gallinaceum*. These results indicate that both test systems have reasonable predictive value in assessing the antimalarial effects of the guanidinopyrimidines.

Evaluation of Prophylactic Action in Chicks. Seven guanidinopyrimidines (**43, 67, 90, 91, 98, 105,** and **115**) were evaluated for prophylactic action in chicks.‡‡,††† White Leghorn cockerels were parasitized by the intrajugular injection of *P. gallinaceum* sporozoites. All control chicks die between 6 and 11 days postinfection. In the present study, the mean survival time of control animals ranged from 7.0 to 7.4 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 five chicks at one to six dose levels ranging from 15 to 480 mg/kg. None of the pyrimidinylguanidines tested possessed prophylactic activity based on the above criteria.

Drug Resistance Studies in Mice. To confirm earlier observations which indicated that the guanidinopyrimidines represented a unique chemical type with regard to apparent mode of action[13-16] (*vide supra*), one of the more promising new compounds, namely 1-(3,4-dichlorophenyl)-3-[4-[(1-ethyl-3-piperidyl)amino]-6-methyl-2-pyrimidinyl]guanidine (**61**), was selected for evaluation against representative drug-resistant lines of *P. berghei* in the mouse. The drug was administered continuously in the diet at levels of 0.0313, 0.008, 0.004, and 0.002% for 6 days to mice infected with the drug-sensitive parent line P and the following drug-resistant lines: line T, completely (>300-fold) resistant to cycloguanil hydrochloride; line S, completely (>600-fold) resistant to 4,4′-sulfonyldianiline (DDS); and line C, 77-fold resistant to chloroquine.‡‡‡ The results (Figure 1) indicate that **61** is essentially fully active against the cycloguanil (T)- and DDS (S)-resistant lines. However, there is definitely some cross resistance against the chloroquine-resistant line C. These results provide further support for the hypothesis that **61** and related pyrimidinylguanidines have a different mode of action from cycloguanil and pyrimethamine. Moreover, **61** lacked appreciable antifolate activity. Thus the growth of *Strep. faecalis* R[21] was not inhibited by **61** at a concentration of 40,000 ng/ml.

Oral Antimalarial Activity in Monkeys. *P. knowlesi* infections were induced in rhesus monkeys by inoculation with 1.0×10^8 parasites/ml.[24],‡‡ Compound **61** was suspended in H_2O and given by gavage to five infected monkeys at a dose of 20 mg/kg per day for 7 days. Three monkeys became negative for asexual forms on day 6, and by day 8 all animals had become negative. However, recrudescence occurred in all five monkeys between days 17 and 19 following parasite-free intervals of 11 to 13 days. Four animals died with malaria between days 20 and 24 with a mean time to death of 22 days. One monkey survived the 35-day experimental period but had intermittant parasitemia. The mean survival time of untreated infected control monkeys was 5.2 days.[24],‡‡

The guanidinopyrimidine **61** was also tested for therapeutic effectiveness against *P. cynomolgi* in the rhesus monkey. *P. cynomolgi* infections were induced in the monkeys by administering 5.0×10^8 parasitized erythrocytes intravenously.[24] The drug was administered by gavage as an aqueous suspension for 7 days. Two monkeys given 10 mg/kg per day became negative for asexual parasites in 6 days but recrudesced on day 17. Three of four monkeys treated at dose levels of 31.6 or 100 mg/kg per day became negative in 3–6 days and were apparently

‡‡Parenteral antimalarial screening against *P. gallinaceum* in chicks was carried out by Dr. Leo Rane at the University of Miami, and test results were supplied through the courtesy of Dr. T. R. Sweeney and Dr. E. A. Steck of the Walter Reed Army Institute of Research.

***For a description of the test method, see ref 20.

†††For a description of the test method, see ref 22.

‡‡‡Testing against resistant strains of *P. berghei* was carried out by Dr. Paul E. Thompson and coworkers, Department of Pharmacology, Parke, Davis and Co., Ann Arbor, Mich. For a description of the test method, see ref 18 and 19.

cured as indicated by failure to become positive 30–31 days after splenectomy on days 33 or 34. The infection was strongly suppressed in the fourth monkey.[24,#]

The guanidinopyrimidine **61** was also effective against the pyrimethamine-resistant chloroquine-susceptable Uganda Palo Alto strain of *P. falciparum* in the owl monkey *Aotus trivirgatus*.[24,#] Each of four animals was cleared of parasites at daily gavage doses of 80 mg/kg per day for 7 days. However, the same dosage regimen had no effect on infections with the Vietnam Monterey strain of *P. falciparum* which are resistant to both chloroquine and pyrimethamine.[24,#]

Toxicological Studies. In view of the remarkable antimalarial properties of the guanidinopyrimidine **61** against both sensitive and drug-resistant plasmodia, the drug was designated for pharmacological and preclinical toxicological studies.[23,#]

Acute Rodent Studies. Results of acute oral toxicity studies showed that the LD_{50} of **61** was 1041 mg/kg (confidence limits 624–1734 mg/kg) in rats, 1128 mg/kg (247–5146 mg/kg) in mice, and 261 mg/kg (157–435 mg/kg) in guinea pigs. Principal toxic effects reported included weight loss, depression, labored respiration, ataxia, ptosis, excessive urination, salivation, and hunched appearance. In an acute intraperitoneal toxicity study, the LD_{50} of **61** was 65.1 mg/kg (confidence limits 33.1–128 mg/kg) in rats, 53 mg/kg (25.6–110 mg/kg) in mice, and 28 mg/kg (11–68 mg/kg) in guinea pigs. Principal toxic effects were similar to those observed in the acute oral toxicity studies.

Subacute Rodent Studies. In a subacute oral toxicity study in rats, **61** was given at dosage levels of 30, 100, and 300 mg/kg per day for 15 days. All high level rats died during the study, but no deaths occurred among animals in the lower dose groups or in the control group.

Salivation following dosing was observed in all test rats, the frequency increasing at each higher treatment level. The incidence of wheezing and/or nasal discharge was higher in the intermediate and high level test groups than in the low level group. Signs of diarrhea were seen in the high level treated group only. Body weight gains and food consumption for the 30 mg/kg animals were slightly lower than, but not significantly different from, those for the controls. Weight gain and food consumption for the 100 mg/kg rats were markedly suppressed.

At the 7-day interval, the per cent of segmented neutrophils, total leukocyte counts, and hematocrit values for the 300 mg/kg test rats were elevated. Blood urea nitrogen and serum glutamic-pyruvic transaminase values for this group were also elevated. Sugar values for the high level group were slightly higher than the control but within normal limits. High prothrombin times were recorded for the control, 30 mg/kg, and 100 mg/kg groups at 7 days and at the terminal interval. All remaining hematological and biochemical values for the control and two lower test groups were within the normal range. The results of urine analyses were also within normal limits and comparable among groups.

The following gross changes in the organs were noted in the majority of the 300 mg/kg animals: a greatly distended stomach containing undigested food, a narrowing at the opening into the duodenum, a thickened duodenum lined with a thick layer of a mucus-like substance, and no fecal material in the small or the large intestine. Small, pale seminal vesicles were found in four high level rats. Microscopic examination of pertinent tissue sections revealed compound-related changes of the lung, kidney, liver, stomach, seminal vesicles, prostate, small intestine, and bone marrow in the high level group and of the lungs, kidney, and stomach in the intermediate level group. A slight increase in the degree and incidence of interstitial pneumonitis was observed at the low level.

Acute and Subacute Dog Studies. In a range finding acute tolerance study in purebred beagle dogs, the drug formulated in gelatin capsules was administered in single oral doses of 10, 15, 20, and 40 mg/kg utilizing two animals at each dose level. The dogs were sacrificed 28 days later. Subacute toxicity studies were then carried out wherein **61** was given orally in gelatin capsules once daily for 14 days to groups of four dogs at doses of 10, 15, and 20 mg/kg per day, with necropsy on days 15 or 16.

Emesis was the only clinical change observed in the acute single dose study. Emesis, diarrhea, and weight loss were the only clinical symptoms noted in the subacute study. The severity of these symptoms was dose dependent. There were no significant hematologic or biochemical changes in either study. Gross and microscopic lesions attributable to a toxic effect of the administered drug were not observed. There were no significant differences in the weights of organs of the treated and untreated control dogs.

Inasmuch as **61** was tolerated relatively well in the above preclinical toxicological studies, the drug has been recommended for human trial.[24,#]

Experimental Section§§§,###

The following intermediates were prepared according to the cited literature references: (3,4-dichlorophenyl)biguanide hydrochloride;[25] 1-(4-hydroxy-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine;[26] 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine;[26] 4-chloro-2-[(p-chlorophenyl)-guanidino]-6-methylpyrimidine;[4] 1-(3,5-dichlorophenyl)-3-(4-hydroxy-6-methyl-2-pyrimidinyl)guanidine.[27]

1-(Substituted phenyl)-3-[4-[[2-(mono- and dialkylamino)alkyl]amino]-6-methyl-2-pyrimidinyl]guanidines. Method A. 1-(3,4-Dichlorophenyl)-3-[4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidine (14). A mixture of 8.8 g (0.0266 mol) of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine, 4.1 g (0.035 mol) of *N,N*-diethylethylenediamine, and 4.6 ml (0.054 mol) of concentrated HCl in 100 ml of EtOH was heated under reflux 16 hr and cooled. The white solid which formed was collected to give 6.8 g of the product as the hydrochloride salt. This was dissolved in H_2O, filtered, and made basic with NaOH. The base was collected and recrystallized from EtOH–H_2O to provide 4.5 g of the product, mp 141–142.5°. The filtrate from the original reaction mixture was poured into 500 ml of H_2O and made basic with NaOH. The solid was collected, dried, and recrystallized from *n*-heptane to provide an additional 2.8 g of the product, mp 141–142.5°.

Method B. 1-(*p*-Chlorophenyl)-3-[4-[[2-(diethylamino)ethyl]-amino]-6-methyl-2-pyrimidinyl]guanidine (2). A mixture of 13.0 g (0.044 mol) of 4-chloro-2-[(*p*-chlorophenyl)guanidino]-6-methylpyrimidine, 6.4 g (0.055 mol) of *N,N*-diethylethylenediamine, and 6 ml of HOAc was heated in an oil bath at 120–130° for 30 min. To this mixture was added 5 ml of concentrated HCl and it was poured into cold H_2O. Insoluble material was removed by filtration, and the filtrate was made strongly alkaline with NaOH, warmed briefly to solidify the gooey precipitate, and filtered. Recrystallization from EtOH–H_2O provided 4.1 g of the product, mp 155–156°.

Method C. 1-(3,4-Dichlorophenyl)-3-[4-[[2-(dipropylamino)-1-methylethyl]amino]-6-methyl-2-pyrimidinyl]guanidine Monohydrochloride Monohydrate (38). A mixture of 8.9 g (0.027 mol) of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine and 4.1 g (0.027 mol) of N^1,N^1-di-*n*-propyl-1,2-propanediamine in 400 ml of C_6H_5Cl, 20 ml of H_2O, and 7.8 g of 50% NaOH was heated under reflux for 20 hr. The reaction mixture was washed several times with cold H_2O, dried over $MgSO_4$, and evaporated *in vacuo* to a yellow oil. This was taken up in 5 *N* HCl and insoluble material was removed by filtration and discarded. The acid solution was poured into excess, cold, dilute

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

###Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

NaOH solution, and the white solid that formed was collected, washed with H_2O, and dried *in vacuo*. The crude product was dissolved in hot EtOAc. The solution was filtered and decanted from a small aqueous layer which separated. Upon cooling, the product (1.2 g) crystallized from the EtOAc as the hydrated hydrochloride salt, mp 150–155°.

1-(3,5-Dichlorophenyl)-3-[4-[[2-(diisopropylamino)ethyl]-amino]-6-methyl-2-pyrimidinyl]guanidine (85). A mixture of 5.0 g (0.015 mol) of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,5-dichlorophenyl)guanidine and 2.2 g (0.015 mol) of *N,N*-diisopropylethylenediamine in 225 ml of C_6H_5Cl, 11 ml of H_2O, and 4.4 g of 50% NaOH was heated under reflux for 17 hr. The cooled mixture was washed with three 250-ml portions of H_2O. The organic layer was dried over K_2CO_3, the solvent was removed *in vacuo*, and the residue was recrystallized from MeCN to give 3.6 of the product, mp 155–157°.

In some cases it was necessary to extract the residue obtained upon removal of the C_6H_5Cl with dilute HCl, filter to remove insoluble material, extract with $CHCl_3$, and then pour the aqueous layer into dilute NaOH to precipitate the product which could then be recrystallized more easily.

Method D. 1-(3,4-Dichlorophenyl)-3-[4-(dimethylamino)-6-methyl-2-pyrimidinyl]guanidine (77). To a solution of 3.5 g (0.027 mol) of 3-amino-1-ethylpiperidine in 50 ml of DMF was added 1.3 g (0.027 mol) of a 50% dispersion of NaH in mineral oil, and the mixture was heated at 60–70° for 4 hr. To this mixture was added dropwise during 25 min a solution of 8.9 g (0.027 mol) of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine in 100 ml of warm DMF. The solution was heated at 75–85° for 41 hr, cooled, diluted with 200 ml of toluene, and washed with two 250-ml portions of H_2O. The organic layer was dried over K_2CO_3 and concentrated *in vacuo* to a semisolid. The residue was dissolved in 250 ml of 5 *N* HCl and filtered. The filtrate was chilled and made basic with concentrated NH_4OH to give 10.9 g of brown solid. This was slurried in EtOH and the insoluble material was collected, treated with hot H_2O, and filtered. The aqueous filtrate was made basic with 2 *N* NaOH and the resulting solid was collected and recrystallized from MeCN to give 1.1 g of the product, mp 175–177°.

Method E. 1-(3,4-Dichlorophenyl)-3-[4-(diethylamino)-6-methyl-2-pyrimidinyl]guanidine Monohydrochloride (78). A mixture of 8.9 g (0.027 mol) of 1-(4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine and 5.9 g (0.027 mol) of 4-amino-2-[(diethylamino)methyl]-1-naphthol in 250 ml of C_6H_5Cl, 20 ml of H_2O, and 7.8 g of 50% NaOH was heated under reflux for 20 hr. The solvent was removed *in vacuo;* the residue was triturated with 250 ml of H_2O and then dissolved in dilute HCl. This solution was treated with charcoal and then made basic with 2 *N* NaOH. The solid formed was triturated with EtOAc and then dissolved in *i*-PrOH saturated with anhydrous HCl. Addition of Et_2O precipitated the product which was recrystallized from MeCN to provide 1.1 g, mp 247–249°.

1,1'-[1,4-Piperazinediylbis[trimethyleneimino(6-methyl-4,2-pyrimidinediyl)]]bis[3-(*p*-chlorophenyl)guanidine] Bis(dimethylformamide) of Crystallization (IX). To a solution of 10.4 g (0.035 mol) of 1-(*p*-chlorophenyl)-3-(4-chloro-6-methyl-2-pyrimidinyl)guanidine and 6 ml of concentrated HCl in 50 ml of EtOH was added a solution of 3.5 g (0.0175 mol) of 1,4-bis(3-aminopropyl)piperazine in 50 ml of EtOH and the mixture was heated under reflux. After 3 days, the solid that had formed was collected and dried. This material (3.0 g) was dissolved in H_2O and made basic with NaOH to yield only a negligible amount of solid. Refluxing was continued for an additional 4 days during which time 5.0 g of solid was formed. Similar treatment of this solid provided 3.2 g of material which was recrystallized from DMF to give 1.23 g (8%) of the product, mp 218–220°. *Anal.* ($C_{34}H_{44}Cl_2N_{14}\cdot 2C_3H_7NO$) C, H, N.

1-(4-Chloro-α,α,α-trifluoro-*m*-tolyl)-3-(4-hydroxy-6-methyl-2-pyrimidinyl)guanidine. To a solution of 19.6 g (0.1 mol) of 4-chloro-α,α,α-trifluoro-*m*-toluidine in 100 ml of 2-ethoxyethanol, 25.4 ml of H_2O, and 8.6 ml of concentrated HCl was added 15.0 g (0.1 mol) of 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine, and the mixture was heated under reflux for 24 hr. A solution was obtained after 2 hr, and then a solid formed gradually. The hot mixture was filtered, and the filtrate was poured into 2 l. of H_2O to yield a second crop. Both crops were slurried in hot MeOH to give a total of 15.9 g (48%) of the product, mp 271–273°. *Anal.* ($C_{13}H_{11}ClF_3N_5O$) C, H, N.

1-(4-Bromo-α,α,α-trifluoro-*m*-tolyl)-3-(4-hydroxy-6-methyl-2-pyrimidinyl)guanidine was prepared similarly to provide a 38.5% yield, mp 262–265°. *Anal.* ($C_{13}H_{11}BrF_3N_5O$) C, H, N.

1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(4-chloro-α,α,α-trifluoro-*m*-tolyl)guanidine. A mixture of 10.9 g (0.03 mol) of 1-(4-chloro-α,α,α-trifluoro-*m*-tolyl)-3-(4-hydroxy-6-methyl-2-pyrimidinyl)guanidine and 25 ml of $POCl_3$ was heated on a steam bath for 45 min. The solution was poured into 600 ml of iced H_2O. The precipitate was collected, washed with H_2O, triturated with NH_4OH, and recrystallized from MeOH to give 4.0 g (36%) of the product, mp 201–203°. *Anal.* ($C_{13}H_{10}Cl_2F_3N_5$) H, N; C: calcd, 42.87; found, 43.29.

1-(4-Bromo-α,α,α-trifluoro-*m*-tolyl)-3-(4-chloro-6-methyl-2-pyrimidinyl)guanidine was prepared similarly in 28% yield, mp 209–210°. *Anal.* ($C_{13}H_{10}BrClF_3N_5$) C, H, N.

1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dimethoxyphenyl)guanidine. (3,4-Dimethoxyphenyl)biguanide was obtained by heating 55.0 g (0.36 mol) of 4-aminoveratrole and 16.9 g (0.2 mol) of dicyandiamide in 200 ml of H_2O and 20 ml of concentrated HCl under reflux for 6 hr. The mixture was filtered, the filtrate was extracted with $CHCl_3$, and the aqueous layer was made strongly basic. The precipitate that separated was recrystallized from MeCN to give 51% yield of the product, mp 194–196° dec. *Anal.* ($C_{10}H_{12}N_5O_2$) C, H, N.

1-(3,4-Dimethoxyphenyl)-3-(4-hydroxy-6-methyl-2-pyrimidinyl)guanidine. To a solution of 24.0 g (0.1 mol) of the above biguanide in 25 ml of 50% aqueous NaOH and 1.5 l. of 80% aqueous EtOH at 45° was added 52.0 g (0.4 mol) of ethyl acetoacetate, and the mixture was stirred at room temperature for 24 hr. The inorganic solid which formed was collected and discarded, and the filtrate was allowed to stand at room temperature for 3 days. The new solid that formed (28.5 g) was washed successively with hot H_2O, boiling MeCN, and hot MeOH to give 15.5 g (51%) of product, mp 259–262°. *Anal.* ($C_{14}H_{17}N_5O_3$) C, H, N.

1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dimethoxyphenyl)guanidine was prepared by chlorination with $POCl_3$ as described above in 28% yield, mp 201–202°, recrystallized from DMF–H_2O. *Anal.* ($C_{14}H_{16}ClN_5O_2$) C, H, N.

1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(4-chloro-1-naphthyl)guanidine. 1-(4-Chloro-1-naphthyl)-3-(4-hydroxy-6-methyl-2-pyrimidinyl)guanidine. A mixture of 17.8 g (0.1 mol) of 1-amino-4-chloronaphthalene, 15.0 g (0.1 mol) of 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine, 200 ml of 2-ethoxyethanol, 25.4 ml of H_2O, and 8.6 ml of concentrated HCl was heated under reflux for 20 hr and filtered. The solid obtained was slurried first in hot MeOH and then in dilute NH_4OH, washed with H_2O, and recrystallized from DMF to give 14.0 g (41%) of the product, mp 278–281°. *Anal.* ($C_{16}H_{14}ClN_5O\cdot 0.85H_2O$) C, H, N, H_2O.

1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(4-chloro-1-naphthyl)guanidine was prepared by chlorination with $POCl_3$ as described above. The crude product was obtained in quantitative yield and was used without purification.

1-(*p*-Butylphenyl)-3-(4-chloro-6-methyl-2-pyrimidinyl)guanidine. 1-(*p*-Butylphenyl)biguanide Monohydrochloride. A suspension of 29.8 g (0.2 mol) of *p*-butylaniline and 17.0 g (0.2 mol) of dicyandiamide in 250 ml of *n*-PrOH containing 20 ml of concentrated HCl was heated under reflux overnight. The solution was chilled and the solid was collected, washed with Et_2O, and dried *in vacuo* to provide 24.5 g (45%) of the product, mp 204.5–209.5°. *Anal.* ($C_{12}H_{19}N_5\cdot HCl$) C, H, N.

1-(*p*-Butylphenyl)-3-(4-hydroxy-6-methyl-2-pyrimidinyl)guanidine was prepared by stirring a mixture of 27.0 g (0.1 mol) of the above biguanide and 30 ml of ethyl acetoacetate in 62 ml of EtOH, 30 ml of H_2O, and 12.4 g (0.155 mol) of 50% aqueous NaOH overnight at room temperature. The solid was collected, stirred with hot MeOH, and dried to give 18.9 g (63%) of the product, mp 224–225°. A sample recrystallized from DMF-H_2O for analysis had mp 227–228°. *Anal.* ($C_{16}H_{21}N_5O$) C, H, N.

1-(*p*-Butylphenyl)-3-(4-chloro-6-methyl-2-pyrimidinyl)guanidine was prepared by chlorination with $POCl_3$ as above in 37% yield, mp 159–160°, after recrystallization from EtOH–H_2O.

1-[*p*-(Benzyloxy)phenyl]-3-(4-chloro-6-methyl-2-pyrimidinyl)-guanidine. 1-[*p*-(Benzyloxy)phenyl]biguanide Monohydrochloride. A mixture of 59.0 g (0.25 mol) of *p*-(benzyloxy)aniline hydrochloride and 22.0 g (0.26 mol) of dicyandiamide in 200 ml of H_2O was heated under reflux for 6 hr and cooled to room temperature. The solid was collected, dissolved in warm MeOH, treated with decolorizing charcoal, and filtered. The hot solution was diluted with an equal volume of *i*-PrOH, allowed to cool, and filtered to provide 44.0 g (55%) of the product, mp 238–240°.

1-[*p*-(Benzyloxy)phenyl]-3-(4-hydroxy-6-methyl-2-pyrimidinyl)guanidine. To a solution of 44.0 g (0.14 mol) of the above

biguanide in 2.5 l. of 80% EtOH containing 20 ml of 50% NaOH at 45° was added 65 ml (0.51 mol) of ethyl acetoacetate. The solution was stirred at room temperature for 24 hr and filtered, and the solid was washed with hot MeOH, hot H_2O, and hot MeCN to give 33.0 g (49%) of the product, mp 259–262°. *Anal.* ($C_{19}H_{19}N_5O_2$) C, H, N.

1-[*p*-(Benzyloxy)phenyl]-3-(4-chloro-6-methyl-2-pyrimidinyl)-guanidine monohydrochloride was prepared by chlorination with $POCl_3$ as above. The crude product was isolated as the HCl salt, mp 222–225°, in 20% yield.

1-(5-Benzyl-4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine. 1-(5-Benzyl-4-hydroxy-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine. To a warm solution of 28.3 g (0.1 mol) of 3,4-dichlorophenylbiguanide hydrochloride in 100 ml of EtOH, 40 ml of H_2O, and 12.4 g (0.155 mol) of 50% NaOH solution was added 66.0 g (0.3 mol) of ethyl 2-benzylacetoacetate. The mixture was stirred overnight at room temperature and filtered. The solid was washed first with hot H_2O and then with hot MeOH and recrystallized from DMF–H_2O to give 4.0 g (10%) of the product, mp 267–268°. *Anal.* ($C_{19}H_{17}Cl_2N_5O$) C, H, N.

1-(5-Benzyl-4-chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine was prepared by chlorination with $POCl_3$. The crude material was obtained in 43% yield.

1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3,4,5-trimethoxyphenyl)guanidine. 1-(4-Hydroxy-6-methyl-2-pyrimidinyl)-3-(3,4,5-trimethoxyphenyl)guanidine. A mixture of 25.3 g (0.14 mol) of 3,4,5-trimethoxyaniline and 20.7 g (0.14 mol) of 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine was stirred under reflux for 3 days in 250 ml of 2-ethoxyethanol containing 12 ml of concentrated HCl and 50 ml of H_2O. The product was collected and washed with hot MeOH and then with hot MeCN. A portion (3.0 g) of the solid was dissolved in about 50 ml of 5 *N* HCl and filtered into 250 ml of dilute NH_4OH. The white solid which formed was collected and triturated with hot H_2O and then with hot MeOH to give 2.3 g of the product, mp 271–275°. Treatment of the remainder of the crude material similarly provided a total yield of 12.8 g (27.4%). *Anal.* ($C_{15}H_{19}N_5O_4$) C, H, N.

1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3,4,5-trimethoxyphenyl)guanidine was prepared by chlorination with $POCl_3$ as above. Reprecipitation of the crude material from DMF by dilute aqueous NaOH gave 30% of the product, mp 195–196°. *Anal.* ($C_{15}H_{18}ClN_5O_3$) C, H, N.

1-(4-Chloro-5,6-dimethyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine. 1-(3,4-Dichlorophenyl)-3-(4-hydroxy-5,6-dimethyl-2-pyrimidinyl)guanidine. A solution of 42.6 g (0.15 mol) of (3,4-dichlorophenyl)biguanide hydrochloride, 43.5 g (0.3 mol) of ethyl 2-methylacetoacetate, and 18.9 g of 50% NaOH in 1.2 l. of MeCN was stirred at room temperature for 24 hr. The solid that formed was collected, washed with H_2O, and boiled with 500 ml of MeCN for 1 hr to give 22.2 g (45%) of the crude product, mp 280–281°.

1-(4-Chloro-5,6-dimethyl-2-pyrimidinyl)-3-(3,4-dichlorophenyl)guanidine was prepared by chlorination with $POCl_3$. The solid obtained by pouring the reaction mixture into iced H_2O was heated for 1 hr in 250 ml of 20% NH_4OH solution to afford a quantitative yield of the product, mp 190–195°, which was used without further purification.

1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorobenzyl)-guanidine. 1-(3,4-Dichlorobenzyl)-3-(4-hydroxy-6-methyl-2-pyrimidinyl)guanidine. A mixture of 6.0 g (0.033 mol) of 3,4-dichlorobenzylamine and 5.0 g (0.033 mol) of 2-(cyanoamino)-4-hydroxy-6-methylpyrimidine in 150 ml of cellosolve and 200 ml of DMF was heated under reflux for 24 hr. The solid which formed on cooling was collected and washed with hot MeOH to give 5.2 g (49%) of the product, mp 291–293° dec. *Anal.* ($C_{13}H_{13}Cl_2N_5O$) C, H, N.

1-(4-Chloro-6-methyl-2-pyrimidinyl)-3-(3,4-dichlorobenzyl)-guanidine. A mixture of 5.0 g (0.015 mol) of the above hydroxy compound and 25 ml of $POCl_3$ was heated under reflux for 45 min. The solution was poured into 750 ml of iced H_2O; the solid was collected, washed with H_2O, and recrystallized from MeOH to provide 4.4 g (85%) of the product, mp 225–227°. *Anal.* ($C_{13}H_{12}Cl_3N_5$) C, H, N.

Aliphatic and Heterocyclic Diamines. The majority of these intermediates were purchased from commercial sources. The following were prepared according to the cited literature: *N,N*-dimethyl-1,4-cyclohexanediamine, *N,N*-diethyl-1,3-cyclohexanediamine, *N,N*-diethyl-1,4-cyclohexanediamine, 3-amino-1-methylpiperidine, 4-amino-1-propylpiperidine, 4-amino-1-isobutylpiperidine, 3-amino-1-isobutylpiperidine, and 1-ethyl-3-(methylamino)-piperidine;[28] N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine;[29] 1-(5-amino-2-ethoxybenzyl)pyrrolidine;[30] 4-amino-α-(diethylamino)-*o*-cresol and 6-allyl-4-amino-α-(diethylamino)-*o*-cresol;[31] 1-ethyl-3-(aminomethyl)pyrrolidine;[32] 1-ethyl-4-(aminomethyl)piperidine and 4-(1-aminoethyl)-1-ethylpiperidine;[33] 4-amino-α^2,α^6-bis(diethylamino)-2,6-xylenol;[34] 2-(*p*-aminophenoxy)ethanol;[35] 1-(*p*-aminophenyl)-4-methylpiperazine;[36] N^{α},N^{α}-diethyltoluene-α,3-diamine and N^{α},N^{α}-diethyltoluene-α,4-diamine.[37]

4-Amino-1-methylpiperidine. A mixture of 98.0 g (0.865 mol) of 1-methyl-4-piperidone, 10.0 g of Raney nickel, and 200 ml of 28% NH_4OH was hydrogenated at 80° for 2.5 hr (initial pressure of 236 kg/cm² at 22°). The catalyst was removed by filtration, and the filtrate was acidified with concentrated HCl. The mixture was concentrated to about 500 ml *in vacuo* and filtered. The filtrate was made strongly alkaline with 50% NaOH and extracted with two 500-ml portions of $CHCl_3$. The extracts were dried, solvent was removed, and distillation yielded 27.8 g (28%) of the product, bp 57–58° (15 mm). *Anal.* ($C_6H_{14}N_2$) H, N; C: calcd, 63.11; found, 62.58.

3-Amino-1-propylpyridinium Bromide. A solution of 10.0 g (0.1 mol) of 3-aminopyridine and 24.6 g (0.2 mol) of *n*-propyl bromide in 100 ml of EtOH was heated under reflux for 24 hr. The solvent was removed *in vacuo*, and the residue was recrystallized first from MeCN and then from *n*-PrOH to give 4.7 g (22%) of the product, mp 165–167°. *Anal.* ($C_8H_{13}BrN_2$) C, H, N. This reaction run on a 2.45-mol scale and omitting the MeCN recrystallization afforded a 45% yield.

3-Amino-1-propylpiperidine. The hydrogenation of 237 g (1.09 mol) of 3-amino-1-propylpyridinium bromide was carried out in 1 l. of HOAc at an initial pressure of 3.58 kg/cm² and an average temperature of 27° over 10.0 g of rhodium on carbon for 24.6 hr. The catalyst was removed, the solvent was removed *in vacuo*, and the residue was dissolved in H_2O. The solution was made strongly basic with 50% NaOH and extracted with Et_2O. Drying, removal of the solvent, and distillation afforded 94.8 g (57%) of the product, bp 74–75° (10 mm), which was shown to be homogeneous by vpc. *Anal.* ($C_8H_{18}N_2$) C, H, N.

***N*-Ethyl-2-methoxy-5-nitrobenzylamine.** To a solution of 10.0 g (0.05 mol) of 2-(chloromethyl)-4-nitroanisole[31] in 75 ml of THF was added 16 ml (0.25 mol) of 71.3% aqueous $EtNH_2$. The reaction mixture was stirred under reflux for 4 hr and then overnight at room temperature. The mixture was poured into 800 ml of H_2O containing excess NaOH. The yellow oil was extracted with C_6H_6, the extracts were washed with H_2O and dried, and the solvent was removed. The residue was taken up in Et_2O and filtered, and HCl was passed into the filtrate. The solid was collected and recrystallized twice from *i*-PrOH to give 3.3 g (28%) of the product, mp 203–205°. *Anal.* ($C_{10}H_{14}N_2O_3 \cdot HCl$) C, H, N.

N^{α}-Ethyl-6-methoxytoluene-α,3-diamine Dihydrochloride. *N*-Ethyl-2-methoxy-5-nitrobenzylamine hydrochloride (330 g, 1.34 mol) in 1.5 l. of MeOH was hydrogenated at 30° and an initial pressure of 3.58 kg/cm² over 10.0 g of Raney nickel. The reaction mixture was filtered into 150 ml of *i*-PrOH saturated with HCl gas. The solvents were removed *in vacuo* leaving a heavy oil which solidified on standing. The solid was triturated with hot *i*-PrOH, powdered with a mortar and pestle, and triturated again with *i*-PrOH to give 275 g (83%) of the product, mp 219–223°. A sample was recrystallized for analysis from a mixture of EtOH and EtOAc. *Anal.* ($C_{10}H_{16}N_2O \cdot 2HCl$) C, H, N, Cl.

***N*-Isobutyl-2-methoxy-5-nitrobenzylamine.** A solution of 200 g (1 mol) of 2-(chloromethyl)-4-nitroanisole and 140 g (2 mol) of isobutylamine in 500 ml of C_6H_6 was heated under reflux for 9 hr. The mixture was cooled to room temperature and washed three times with H_2O, the C_6H_6 layer was dried over K_2CO_3, and the solvent was removed *in vacuo*. The residue was taken up in 1.5 l. of Et_2O and HCl was passed into the solution to yield 232 g (84.5%) of the product. A sample recrystallized from *i*-PrOH for analysis gave mp 176–179°. *Anal.* ($C_{12}H_{18}N_2O_3 \cdot HCl$) C, H, N, Cl^-.

N^{α}-Isobutyl-6-methoxytoluene-α,3-diamine. A solution of 222 g (0.9 mol) of *N*-isobutyl-2-methoxy-5-nitrobenzylamine hydrochloride in 1.2 l. of MeOH was hydrogenated over 10.0 g of Raney nickel for 25 hr at an initial pressure of 3.58 kg/cm² and average temperature of 28°. The mixture was filtered into 100 ml of *i*-PrOH saturated with HCl. The solvent was removed *in vacuo* to leave a brown oil which could not be induced to crystallize and was used without characterization.

***N*-Isopropyl-2-methoxy-*N*-methyl-5-nitrobenzylamine** was prepared similarly to the isobutyl analog above in 55% yield, mp

155–157°, after recrystallization from a mixture of *i*-PrOH and petroleum ether. *Anal.* ($C_{12}H_{18}N_2O_3 \cdot HCl \cdot 0.33H_2O$) C, H, N, H_2O.

N^{α}-Isopropyl-6-methoxy-N^{α}-methyltoluene-α,3-diamine. The above nitro compound (100 g, 0.35 mol) was hydrogenated in 500 ml of MeOH over 3.0 g of Raney nickel at an initial pressure of 3.58 kg/cm² at 27° for 44.5 hr. The mixture was filtered into 52 ml of *i*-PrOH saturated with gaseous HCl, the solvent was removed *in vacuo*, and the residue was triturated with hot *i*-PrOH to give 68.0 g (68%) of the product, mp 234–236°. *Anal.* ($C_{12}H_{20}N_2O \cdot 2HCl \cdot 0.1H_2O$) C, H, N, H_2O; Cl^-: calcd, 25.05; found, 24.35.

1-(2-Methoxy-5-nitrobenzyl)-4-methylpiperazine. A solution of 10.0 g (0.05 mol) of 2-(chloromethyl)-4-nitroanisole and 10.0 g (0.10 mol) of 1-methylpiperazine in 40 ml of C_6H_6 was heated under reflux for 3 hr and allowed to remain at room temperature overnight. 1-Methylpiperazine hydrochloride was removed by filtration and solvent was removed from the filtrate *in vacuo*. The residue was dissolved in 125 ml of Et_2O and filtered. Upon standing for a short time the product, 6.8 g (50%), mp 81–83°, was deposited. *Anal.* ($C_{13}H_{19}N_3O_3$) C, H; N: calcd, 15.84; found, 15.39.

1-(5-Amino-2-methoxybenzyl)-4-methylpiperazine. A solution of 85.0 g (0.32 mol) of the above nitro compound in 850 ml of MeOH was hydrogenated over 5.0 g of Raney nickel at 3.58 kg/cm² for 250 hr. The mixture was filtered into 150 ml of 30% HCl–*i*-PrOH. Solvent was removed *in vacuo*, and the dark brown viscous residue was used without further purification.

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References

(1) E. F. Elslager, J. Johnson, and L. M. Werbel, *J. Heterocycl. Chem.*, **10**, 611 (1973).
(2) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 729 (1946).
(3) P. E. Thompson and L. M. Werbel, "Antimalarial Agents, Chemistry and Pharmacology," Academic Press, New York, N. Y., 1972.
(4) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 362 (1946).
(5) F. H. S. Curd, D. G. Davey, and F. L. Rose, *Ann. Trop. Med. Parasitol.*, **39**, 157 (1945).
(6) F. H. S. Curd, D. G. Davey, and F. L. Rose, *ibid.*, **39**, 139 (1945).
(7) J. Singh, A. P. Ray, P. C. Basu, and C. P. Nair, *Trans. Roy. Soc. Trop. Med. Hyg.*, **46**, 639 (1952).
(8) A. R. D. Adams and G. Sanderson, *Ann. Trop. Med. Parasitol.*, **39**, 165 (1945).
(9) A. R. D. Adams and G. Sanderson, *ibid.*, **39**, 169 (1945).
(10) A. R. D. Adams and G. Sanderson, *ibid.*, **39**, 173 (1945).
(11) A. R. D. Adams and G. Sanderson, *ibid.*, **39**, 180 (1945).
(12) F. H. S. Curd, D. G. Davey, and F. L. Rose, *ibid.*, **39**, 208 (1945).
(13) J. Williamson, D. S. Bertram, and E. M. Lourie, *Nature (London)*, **159**, 885 (1947).
(14) J. Williamson and E. M. Lourie, *Ann. Trop. Med. Parasitol.*, **41**, 278 (1947).
(15) J. P. Thurston, *Parasitology*, **43**, 246 (1953).
(16) J. Singh, C. P. Nair, and A. P. Ray, *Indian J. Malariol.*, **8**, 187 (1954).
(17) W. H. Cliffe, F. H. S. Curd, F. L. Rose, and M. Scott, *J. Chem. Soc.*, 574 (1948).
(18) P. E. Thompson, A. Bayles, and B. Olszewski, *Exp. Parasitol.*, **25**, 32 (1969).
(19) P. E. Thompson, A. Bayles, and B. Olszewski, *Amer. J. Trop. Med. Hyg.*, **19**, 12 (1970).
(20) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(21) J. Davoll, A. M. Johnson, H. J. Davies, O. D. Bird, J. Clarke, and E. F. Elslager, *ibid.*, **15**, 812 (1972).
(22) L. Rane and D. S. Rane, *Proc. Helminthol. Soc. Washington*, **39**, 283 (1972).
(23) M. A. Silver and D. M. Aviado, *Exp. Parasitol.*, **24**, 152 (1969).
(24) T. R. Sweeney and D. P. Jacobus, Abstracts of Papers, 12th National Medicinal Chemistry Symposium of the American Chemical Society, Seattle, Wash., June 22–25, 1970, pp 7d, 7z.
(25) E. J. Modest and P. Levine, *J. Org. Chem.*, **21**, 14 (1956).
(26) F. H. S. Curd and F. L. Rose, British Patent 581,334 (Oct 9, 1946).
(27) F. H. S. Curd and F. L. Rose, British Patent 581,345 (Oct 9, 1946).
(28) L. M. Werbel, A. Curry, E. F. Elslager, and C. Hess, *J. Heterocycl. Chem.*, **10**, 363 (1973).
(29) R. L. Bent, J. C. Dessloch, F. C. Duennebier, D. W. Fassett, D. B. Glass, T. H. James, D. B. Julian, W. R. Ruby, J. M. Snell, J. H. Sterner, J. R. Thirtle, P. W. Vittum, and A. Weissberger, *J. Amer. Chem. Soc.*, **73**, 3100 (1951).
(30) E. F. Elslager and N. F. Haley, *J. Heterocycl. Chem.*, **6**, 105 (1969).
(31) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Amer. Chem. Soc.*, **70**, 1363 (1948).
(32) H. C. Scarborough, J. L. Minielli, B. C. Lawes, W. G. Lobeck, Jr., J. R. Corrigan, and Y.-H. Wu, *J. Org. Chem.*, **26**, 4955 (1961).
(33) Belgian Patent 706,646 (May 16, 1968).
(34) V. I. Stavrovskaya, *J. Gen. Chem. USSR*, **25**, 915 (1955).
(35) A. J. Shukis and R. C. Tallman, *J. Amer. Chem. Soc.*, **66**, 1461 (1944).
(36) H. Loewe, H. Mieth, and J. Urbanietz, *Arzneim.-Forsch.*, **16**, 1306 (1966).
(37) G. M. Bennett and G. H. Willis, *J. Chem. Soc.*, 131, 256 (1929).