Folate Antagonists. 3. 2,4-Diamino-6-(heterocyclic)quinazolines, a Novel Class of Antimetabolites with Potent Antimalarial and Antibacterial Activity†,‡,[2]

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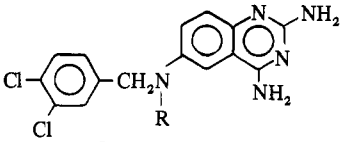
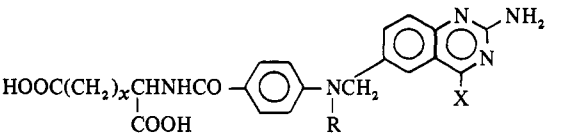
Eleven 2,4-diamino-6-(heterocyclic)quinazolines (VI) were prepared by condensing 5-chloro-2-nitrobenzonitrile (III) with the appropriate saturated heterocycle to give the corresponding 5-(heterocyclic)-2-nitrobenzonitriles (IV) (24–94%), followed by $SnCl_2 \cdot 2H_2O$ reduction to the 2-amino-5-(heterocyclic)-benzonitriles (V) (51–85%) and cyclization to VI (6–71%) with chloroformamidine·HCl or cyanoguanidine. The reaction of 2,4;6-triaminoquinazoline (**33**) with 2,5-diethoxytetrahydrofuran, acetonylacetone, phthalic anhydride, and α,α'-dibromoxylene afforded 2,4-diamino-6-(pyrrol-1-yl)quinazoline (**34**), 2,4-diamino-6-(2,5-dimethylpyrrol-1-yl)quinazoline (**35**), *N*-(2,4-diamino-6-quinazolinyl)phthalimide (**36**), and 2,4-diamino-6-(2-isoindolinyl)quinazoline (**37**) in 26–85% yield. 2,4-Diamino-6-(3,5-dimethylpyrazol-1-yl)quinazoline (**40**) (63%) was prepared from 2,4-diamino-6-hydrazinoquinazoline (**39**) by cyclization with acetylacetone. Ring closure of 2,4,6,8-tetraaminoquinazoline (**43**) and 2,4-diamino-6-(aminomethyl)-quinazoline (**46**) utilizing acetonylacetone gave 2,4-diamino-6,8-bis(2,5-dimethylpyrrol-1-yl)quinazoline (**44**) (53%) and 2,4-diamino-6-[(2,5-dimethylpyrrol-1-yl)methyl]quinazoline (**47**) (69%), respectively. Thirteen heterocyclic quinazolines were active orally or parenterally against *Plasmodium berghei* in mice and *P. gallinaceum* in chicks. 2,4-Diamino-6-(2-phenyl-1-pyrrolidinyl)quinazoline (**27**) and 2,4-diamino-6-(2-benzylpiperidino)quinazoline (**31**) showed activity comparable with or superior to cycloguanil hydrochloride and 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]quinazoline (Ib). Many of the heterocyclic quinazolines were also highly active against a broad spectrum of pathogenic and nonpathogenic bacteria *in vitro*. 2,4-Diamino-6-(2,5-dimethylpyrrol-1-yl)quinazoline (**35**) exhibited good activity against *Streptococcus pyogenes* (C-203) in mice following single oral or sc doses ranging from 50 to 500 mg/kg, and the drug was synergistic with sulfamethoxypyridazine.

In recent communications from these laboratories relating to folate antagonists,[1-8] it was reported that various 2,4-diamino-6-{[aralkyl and (heterocyclic)methyl]amino- and -nitrosamino}quinazolines, exemplified by 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (Ia)[1,3] and 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]quinazoline (Ib),[4-6] exhibit strong antimalarial activity against sensitive and drug-resistant lines of *Plasmodium berghei* in mice, *P. gallinaceum* in chicks, and *P. cynomolgi* and *P. knowlesi* in rhesus monkeys.[1,3,4,6] These substances also possess an encouraging degree of activity against *Trypanosoma cruzi* in chick embryo cell cultures and in mice[1,3,5,6] and are potent folate antagonists in bacterial systems.[1,6] In contradistinction, various 2,4-diamino- and 2-amino-4-hydroxyquinazoline Glu and Asp analogs[7] (II, where $x = 1$ or 2; R = H or CH_3; and X = OH or NH_2) lack appreciable antiparasitic activity, but display potent inhibitory effects against *Streptococcus faecalis* R (ATCC 8043)[8] [*Strep. faecium* var. *durans* (SF/0)],[9] thymidylate synthetase and dihydrofolic reductase from mammalian and bacterial sources,[8] several sublines of the L1210 mouse leukemia,[9] and L1210 cells in culture.[9]



Ia, R = H
b, R = NO

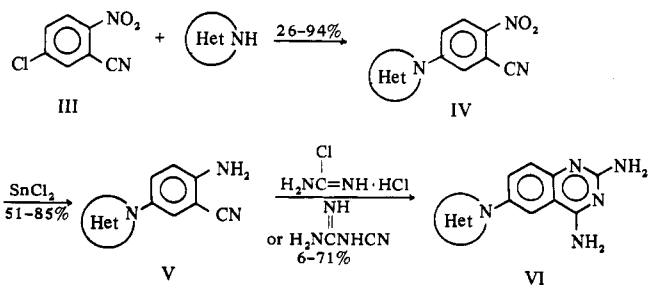


II

We now report the synthesis and biological properties of various 2,4-diamino-6-(heterocyclic)quinazolines (VI), a novel series of antimetabolites with potent antimalarial and antibacterial activity.

Chemistry. Many of the 2,4-diamino-6-(heterocyclic)-quinazolines (VI) were prepared utilizing the route exemplified by Scheme I. The condensation of 5-chloro-2-nitrobenzonitrile (III) with the appropriate saturated heterocycle in 2-ethoxyethanol or DMSO afforded the corresponding 5-(heterocyclic)-2-nitrobenzonitriles (IV, **1–10**, Table I) in 26–94% yield (procedures I, II). Reduction of the nitro-

Scheme I



III IV V VI

†This is paper 25 of a series on antimalarial drugs. For paper 24, see ref 1.

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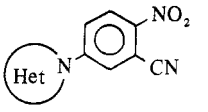
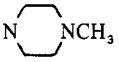
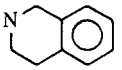
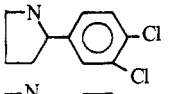
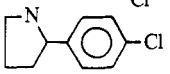
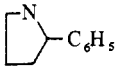
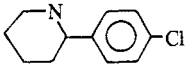
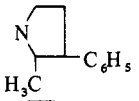
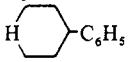
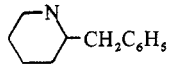
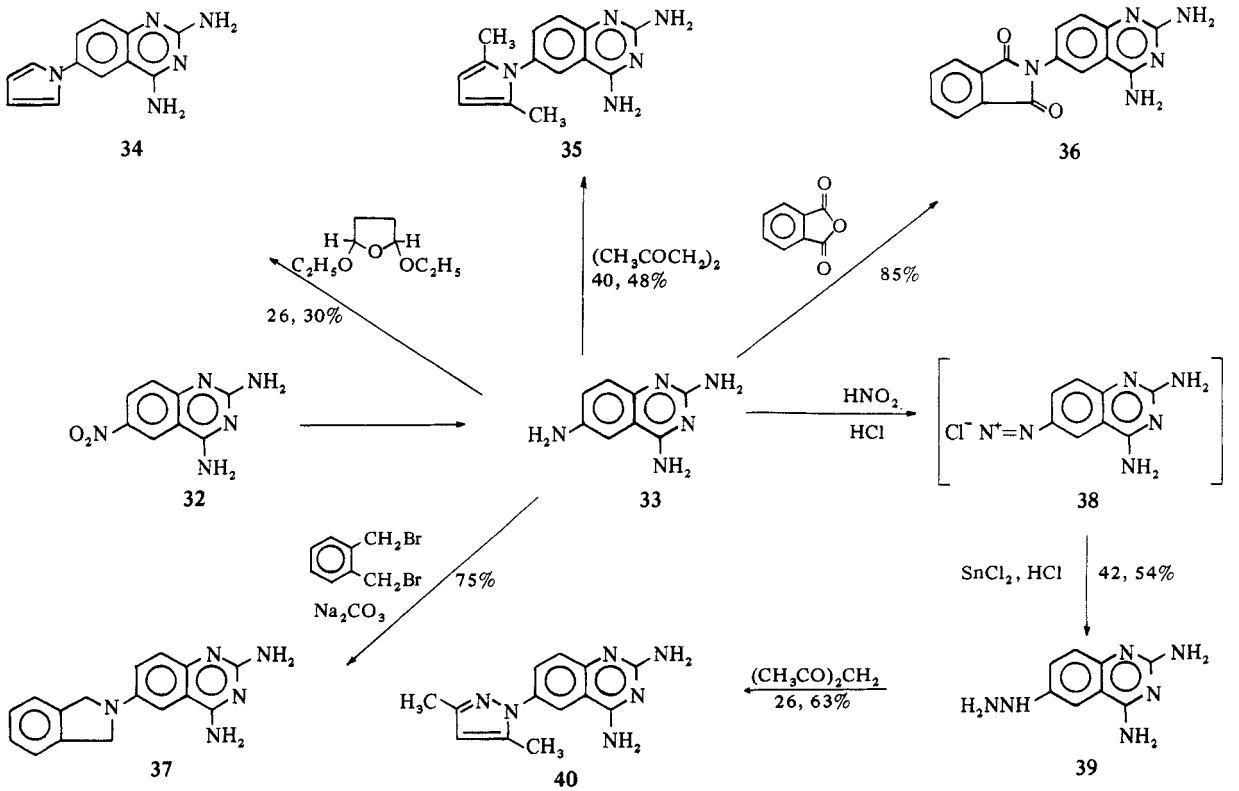
Table I. 5-(Heterocyclic)-2-nitrobenzonitriles



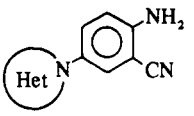
No.	Het N	Mp, °C	Yield purified, %	Purificn solvent	Procedure	Formula	Analyses
1		127-128	94	EtOH	I	$C_{12}H_{13}N_3O_2$	C, H, N
2		161-163	85	EtOH	I	$C_{12}H_{14}N_4O_2$	C, H, N
3		180-182	76	MeCN	I	$C_{16}H_{13}N_3O_2$	C, H, N
4		188-191	67	DMSO	II	$C_{17}H_{13}Cl_2N_3O_2$	C, H, N
5		189-192	90	MeCN	II	$C_{17}H_{14}ClN_3O_2$	C, H, N
6		188-191	77	DMSO	II	$C_{17}H_{15}N_3O_2$	C, H, N
7		162-164	39	EtOH	II	$C_{18}H_{16}ClN_3O_2$	C, H, N
8		186-187	26	EtOH	I	$C_{18}H_{17}N_3O_2 \cdot 0.1H_2O$	C, H, N, H_2O
9		220-222	86	DMF-H_2O	I	$C_{18}H_{17}N_3O_2$	C, H, N
10		120-126	47	EtOH	II	$C_{19}H_{19}N_3O_2$	C, H, N

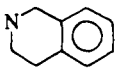
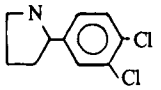
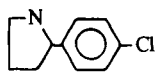
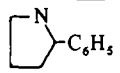
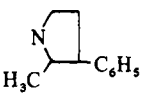
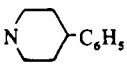
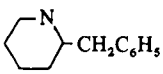
Scheme II



benzonitriles (IV) with $SnCl_2 \cdot 2H_2O$ in aqueous HCl or aqueous HCl-HOAc gave the 2-amino-5-(heterocyclic)benzonitriles (V, **11-20**, Table II) in 51-85% yield (procedures III-V). Cyclization of the requisite aminobenzonitrile (V) with chloroformamidine hydrochloride[10] in dry diglyme (procedure VI) or with cyanoguanidine in concd HCl (pro-

Table II. 2-Amino-5-(heterocyclic)benzonitriles



No.	Het N	Mp, °C	Yield purified, %	Purifcn solvent	Procedure	Formula	Analyses
11		92–94	72	CCl_4–petr ether	III	$C_{12}H_{15}N_3$	C, H, N
12		98–100	84	CCl_4	IV	$C_{12}H_{16}N_4$	C, H, N
13		117–120	58	EtOH–H_2O	V	$C_{14}H_{19}N_3$	C, H, N
14		128–130	85	*i*-PrOH	V	$C_{16}H_{15}N_3$	C, H, N
15		134–136	56	*i*-PrOH	V	$C_{17}H_{15}Cl_2N_3$	C, H, N
16		135–137	51	*i*-PrOH	V	$C_{17}H_{16}ClN_3$	C, H, N
17		217–221	68	EtOH–Et_2O	V	$C_{17}H_{17}N_3 \cdot HCl$	C, H, Cl^-, N
18		143–144	61	EtOH–H_2O	V	$C_{18}H_{19}N_3 \cdot 0.06H_2O$	C, H, N, H_2O
19		166–167	79	*i*-PrOH	V	$C_{18}H_{19}N_3$	C, H, N
20		104–105	75	EtOH–H_2O	V	$C_{19}H_{21}N_3$	C, H, N

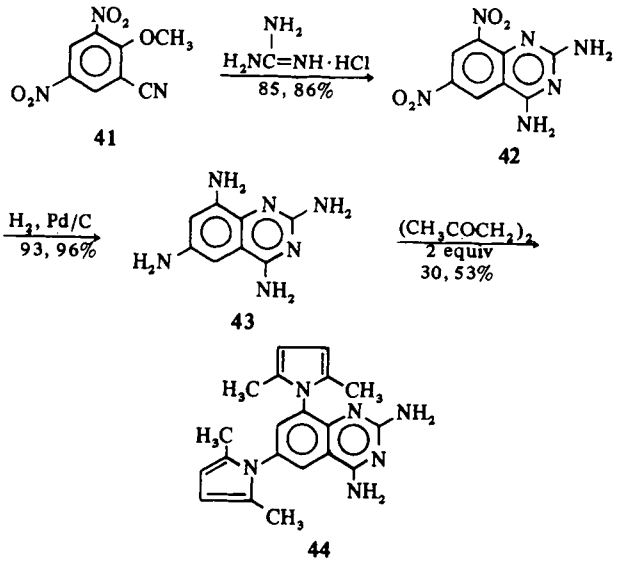
cedure VII) gave the desired 2,4-diamino-6-(heterocyclic)-quinazolines (V, **21–31**, Table III) (6–71%).

Alternatively, various 2,4-diamino-6-(heterocyclic)quinazolines were synthesized from 2,4,6-triaminoquinazoline (**33**)[7] *via* 2,4-diamino-6-nitroquinazoline (**32**)[7] (Scheme II). Thus the condensation of **33** with 2,5-diethoxytetrahydrofuran, acetonylacetone, phthalic anhydride, and α,α'-dibromo-*o*-xylene afforded 2,4-diamino-6-(pyrrol-1-yl)quinazoline (**34**) (26, 30%), 2,4-diamino-6-(2,5-dimethylpyrrol-1-yl)quinazoline (**35**) (40, 48%), *N*-(2,4-diamino-6-quinazolinyl)phthalimide (**36**) (85%), and 2,4-diamino-6-(2-isoindolinyl)quinazoline (**37**) (75%), respectively. Diazotization of **33** gave the diazonium salt **38**, which was reduced *in situ* with $SnCl_2 \cdot 2H_2O$ to give 2,4-diamino-6-hydrazinoquinazoline (**39**) (42, 54%). Cyclization of **39** with acetylacetone afforded 2,4-diamino-6-(3,5-dimethylpyrazol-1-yl)quinazoline (**40**) (26, 63%).

2,4-Diamino-6,8-bis(2,5-dimethylpyrrol-1-yl)quinazoline (**44**) was readily synthesized starting from 3,5-dinitro-*o*-anisonitrile (**41**)[11] (Scheme III). Ring closure of **41** with guanidine hydrochloride gave 2,4-diamino-6,8-dinitroquinazoline (**42**) in high yield (85, 86%). Hydrogenation of **42** over 10% Pd/C afforded 2,4,6,8-tetraaminoquinazoline (**43**) (93, 96%), which was condensed with 2 equiv of acetonylacetone to give 2,4-diamino-6,8-bis(2,5-dimethylpyrrol-1-yl)-quinazoline (**44**) (30, 53%).

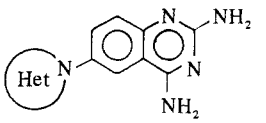
2,4-Diamino-6-[(2,5-dimethylpyrrol-1-yl)methyl]quinazoline (**47**), the methylene homolog of **35**, was also prepared starting from 2,4,6-triaminoquinazoline (**33**)[7] (Scheme IV).

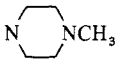
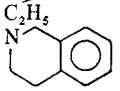
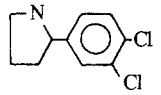
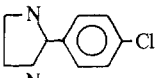
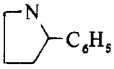
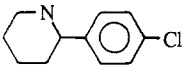
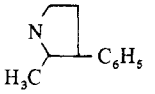
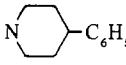
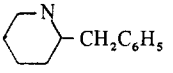
Scheme III



The triamine was first converted *via* the Sandmeyer reaction to the known 2,4-diamino-6-quinazolinecarbonitrile (**45**),[7] which was hydrogenated over Raney Ni at 70–75° (100 atm) to give 2,4-diamino-6-(aminomethyl)quinazoline (**46**) in 53–82% yield. Cyclization of **46** with acetonylacetone afforded the desired product (**47**) in 60–69% yield. Spectral data (ir, uv, nmr) were in agreement with the structures shown for each of the 2,4-diamino-6-(heterocyclic)quinazolines.

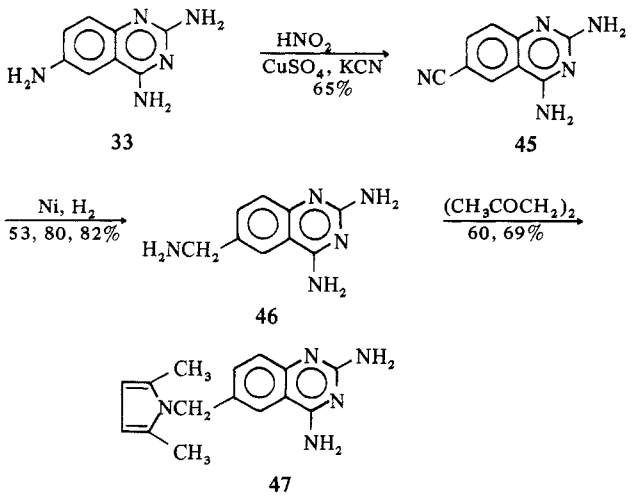
Table III. 2,4-Diamino-6-(heterocyclic)quinazolines *via* 5-Chloro-2-nitrobenzonitrile



No.	Het N	Mp, °C	Yield purified, %	Purificn solvent	Procedure	Formula	Analyses
21		292–294	40	EtOH–H_2O	VI	$C_{13}H_{17}N_5$	C, H, N
22		286–292	71	$C_2H_5OCH_2CH_2OH$–H_2O	VI	$C_{13}H_{18}N_6$	C, H, N
23		320–323	29	EtOH–H_2O	VI	$C_{15}H_{21}N_5 \cdot HCl \cdot 0.05H_2O$	C, H, Cl^-, N, H_2O
24		248–251	34	MeOH	VII	$C_{17}H_{17}N_5 \cdot 2C_7H_8O_3S$[a]	C, H, N, S
25		149–152	37	*i*-PrOH–MeCN	VI	$C_{18}H_{17}Cl_2N_5$	C, H, N
26		145–147	45	*i*-PrOH–MeCN	VI	$C_{18}H_{18}ClN_5$	C, H, N
27		246–247	26	EtOH	VII	$C_{18}H_{19}N_5 \cdot 0.5H_2O$	C, H, N
28		200–205 dec	21	*i*-PrOH–MeCN	VI	$C_{19}H_{20}ClN_5$	H, N; C[b]
29		>300	44	DMF	VI	$C_{19}H_{21}N_5 \cdot HCl$	C, H, Cl^-, N
30		255–257 dec	28	MeOH	VII	$C_{19}H_{21}N_5$	C, H, N
31		108–112	6	EtOH	VI	$C_{20}H_{23}N_5 \cdot 0.25H_2O$	C, H, N, H_2O

[a] $C_7H_8O_3S$ represents *p*-toluenesulfonic acid. [b] C: calcd, 64.5; found, 63.9.

Scheme IV



33 45 46 47

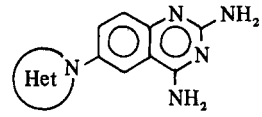
The pyrrolidine, piperidine, and piperazine intermediates required for the synthesis of compound **21–24, 30,** and **31** are commercially available. 2-(3,4-Dichlorophenyl)pyrrolidine, 2-(*p*-chlorophenyl)pyrrolidine,[12] and 2-phenylpyrrolidine[13] were obtained by the reaction of the requisite phenylmagnesium bromide and 4-chlorobutyronitrile to give the corresponding 2-phenyl-1-pyrrolines,[13] which were hydrogenated over 5% Pt/C. 2-(*p*-Chlorophenyl)piperidine was prepared by the condensation of *p*-chlorophenylmagnesium bromide with 5-chlorovaleronitrile to give 2-(*p*-chlorophenyl)-3,4,5,6-tetrahydropyridine,[14] followed by hydrogenation in HOAc over Pt/C. Attempts to reduce 2-methyl-3-phenyl-1-pyrroline to 2-methyl-3-phenylpyrrolidine with $NaBH_4$ were unsuccessful, but catalytic hydrogenation utilizing Pt/C afforded the intermediate 2-methyl-3-phenylpyrrolidine.

Antimalarial Effects. Antimalarial studies with the 2,4-diamino-6-(heterocyclic)quinazolines described in the present communication were carried out utilizing *P. berghei* in mice and *P. gallinaceum* in chicks. Compounds **23, 25, 26, 28, 29,** and **31** were administered sc in a single dose to mice infected with *P. berghei*[§,#] (Table IV). Five substances (**23, 25, 26, 28, 31**) cured all of the mice at one or more dose levels ranging from 40 to 640 mg/kg, but four of them, like cycloguanil hydrochloride, were toxic for mice at the higher dose levels. 2,4-Diamino-6-(2-benzylpiperidino)quinazoline (**31**), the most promising member of the series, exhibited activity comparable with or superior to cycloguanil hydrochloride, 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (Ia), and 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]quinazoline (Ib).

§ The parenteral antimalarial screening was carried out by Dr. Leo Rane of the University of Miami, and test results were provided through the courtesy of Dr. David P. Jacobus, 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 15.

Table IV. Parenteral Effects of 2,4-Diamino-6-(heterocyclic)quinazolines against *Plasmodium berghei* in Mice



No.[d]	ΔMST; T or C[a] after single mg/kg dose						
	640	320	160	80	40	20	10
23	T5	C5	C5	13.7; Cl	8.9	3.3	0.7
		C5	C5	13.4; Cl	8.7	3.1	
25	T5	C2, T3	C2, T3	C5	9.9; C4	7.5	2.5
		C2, T3	C2, T3	C5	20.4; C3	7.7	
26	C2, T3	C2, T3	C4, T1	C5	20.9; C3	18.2; C2	7.7
		C2, T3	C4, T1	C5	17.9; C4	21.1; C1	
28		T5	C2, T3	C5	C5	7.5	4.3[b]
			C1, T4	C5	C5	7.3	4.5
29	1.9	0.5	0.5	0.3	0.3	0.3	
31	C5	C5	C5	C5	C5	9.9; C3	6.7[c]
		C5	C5	C5	C5	11.4; C3	6.9
					C5	12.4; C3	
Cycloguanil hydrochloride	T5	C3, T2	C5	21.6; C2	13.4; C1	7.9	4.9
		C2, T3	C5	21.9; C2	13.4; C1	8.1	
Ia acetate	C5	C5	9.9; C3	12.9	7.1	2.5	0.7
		C5	9.9; C3	13.1	7.3	2.7	0.7
Ib acetate		C5		C5		22.4; C1	

[a] 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 was 6.1 days. T signifies the number of toxic deaths, occurring on days 2–5 after infection, which are attributed to drug action. C indicated the number of mice surviving at 60 days post infection and termed "cured"; data to establish parasitological cure based on subinoculation are unavailable. Each compound was administered as a single sc dose. Each entry at each dose level represents results with a 5 animal group. [b] ΔMST at 5 mg/kg = 2.7 days; [c] ΔMST = 5.1 days at 5 mg/kg, 1.7 days at 2.5 mg/kg, and 0.5 days at 1.25 mg/kg. [d] Structures for het N are given in Table III.

Twelve compounds (**21, 22, 24, 27, 30, 34–37, 40, 44, 47**) were given by gavage for 4 days or continuously by drug-diet for 6 days to mice infected with another normal drug-sensitive strain of *P. berghei***,†† (Table V). Among them, seven quinazolines (**21, 24, 27, 30, 34, 44, 47**) produced a 90% suppression of the parasitemia at daily oral doses ranging from 0.35 to 16 mg/kg. 2,4-Diamino-6-(2-phenyl-1-pyrrolidinyl)quinazoline (**27**), the outstanding member of the group, was approximately 210 times as potent as quinine hydrochloride and compared favorably with 2,4-diamino-[6-(3,4-dichlorobenzyl)nitrosamino]quinazoline (Ib).[4,6]

Several of the heterocyclic quinazoline derivs (**23, 25, 26**) were also evaluated against *P. gallinaceum* infections in white Leghorn cockerels.‡‡ Chicks were given an iv injection of 0.2 ml of heparinized blood infected with *P. gallinaceum* and having a minimum of 80–90% parasitized red blood cells. The parasitized blood was drawn by cardiac puncture from donor birds infected 72 hr earlier with *P. gallinaceum.* Donor strains were maintained in separate groups of chicks, 14–16 days old, that also received inoculations of heparinized infected blood. In every experiment 100% of the untreated control birds died within 72–96 hr postinfection. Candidate substances were administered to chicks in a single sc dose in peanut oil immediately after infection. In this test, as in the mouse test, 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 controls. A compd was arbitrarily considered to be active against malaria if it produced increases in the survival times of treated chicks that were at least 100% over the survival times of untreated controls. As indicated in Table VI, all these substances were active based on these criteria and each prolonged the survival time of chicks for periods of 3.8–16.0 days following a single sc or iv dose ranging from 7.5 to 160 mg/kg. However, none was as promising as cycloguanil hydrochloride or the two diaminoquinazoline reference drugs (Table VI).

Antibacterial Studies. Each of the 2,4-diamino-6-(heterocyclic)quinazolines was tested *in vitro* against a spectrum of pathogenic bacteria including *Streptococcus faecalis* (MGH-2), normal (UC-76) and drug-resistant (S18713) *Staphylococcus aureus, Pseudomonas aeruginosa* (28), *Escherichia coli* (Vogel), and *Shigella sonnei* (C-10). A modification of the gradient plate procedure of Szybalski[16] and Webb and Washington[17] was employed throughout. Fourteen compounds were active against *Strep. faecalis* (MGH-2) at <0.25 μg/ml, eight against *Staph. aureus* (UC-76) at <0.25 μg/ml, six against *Staph. aureus* (S18713) at <0.25 μg/ml, five against *E. coli* (Vogel) at 1–10 μg/ml, and five against *S. sonnei* (C-10) at 1.5–20 μg/ml (Table VII). None was active against *Ps. aeruginosa* (28) at 25 μg/ml, and **44** was ineffective against all organisms at 25 μg/ml. Four substances (**34, 35, 40,** and **47**) were tested for their antibacterial effects in mice utilizing published procedures.[18] The most promising substance, 2,4-diamino-6-(2,5-dimethylpyrrol-1-yl)quinazoline (**35**), exhibited good activity against *Strep. pyogenes* (C-203) in mice following single oral or sc doses ranging from 50 to 500 mg/kg, and the drug was synergistic with sulfamethoxypyridazine.

Antitrypanosomal Evaluation. In view of the marked activity of the benzylaminoquinazolines Ia and b against *T. cruzi* in chick embryo cell (CEC) cultures and in mice,[1,3,5] several of the 2,4-diamino-6-(heterocyclic)quinazolines (**21, 22, 34–36, 40, 47**) were evaluated in these test systems. As in earlier work,[1,3,5] a Brazilian strain of *T. cruzi* was util-

**Selected compounds were kindly studied orally against *P. berghei* in mice 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 3 and 4.

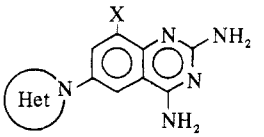
‡‡Antimalarial screening against *Plasmodium gallinaceum* in chicks was carried out by Dr. Leo Rane at the University of Miami, and test results were supplied through the courtesy of Dr. David P. Jacobus, Dr. T. R. Sweeney, and Dr. E. A. Steck of the Walter Reed Army Institute of Research.

ized for studies both in culture and in mice. Details of the test procedures were reported previously.[1,3,5]

Five compds (**21, 22, 34, 35, 40**) were tested in CEC cultures. When incubated for periods of either 48 or 72 hr, four compds (**21, 34, 35, 40**) were active against *T. cruzi* at one or more drug concns, ranging from 6.25 to 25 μg/ml, that were usually not cytotoxic for chick embryo cells. This activity was reflected by inhibition of extracellular growth, of cell invasion, and of intracellular multiplication. However, none was more potent than Ia and b reported previously.[1,3,5] Substances **21, 34-36, 40**, and **47** were administered continuously in the diet of mice infected with *T. cruzi* for 14 days. None exhibited significant activity even at maximum tolerated dose levels.

Antimetabolite Studies. In anticipation that antimetabolite studies utilizing bacterial systems might assist in clarifying relationships between structure, antiparasitic activity, and antibacterial effects within this series, several of the 2,4-diamino-6-(heterocyclic)quinazolines (**21, 22, 24, 30, 34-37, 40, 44, 47**) were evaluated as inhibitors of *Strep. faecalis* R (*Strep. faecium* var. *durans*, ATCC 8043), *Strep. faecalis* A (methotrexate-, aminopterin-resistant mutant), and *Lacto-*

Table V. Oral Effects of 2,4-Diamino-6-(heterocyclic)quinazolines against *Plasmodium berghei* in Mice



No.[d]	X	Route[a]	Days	No. of mice	SD_{90},[b] mg/kg per day	Q[c]
21	H	D	6	28	<6.7	>11
22	H	D	6	7	>350	<0.2
24	H	D	6	28	4.6	16
27	H	D	6	28	0.35	210
30	H	D	6	14	16	4.6
34	H	G	4	10	11	6.4
35	H	G	4	10	>10	<7.4
36	H	D	6	7	>300	<0.2
37	H	D	6	14	>36	<2.0
40	H	G	4	10	>40	<1.8
44	*e*	D	6	14	16	4.6
47	H	D	6	21	<13	>5.9
Quinine hydrochloride		D	6	224	74.5	1
		G	4	59	74.0	1
Cycloguanil hydrochloride		D	6	40	2.1	35
Pyrimethamine		D	6	42	0.28	270
Trimethoprim		D	6	21	120	0.6
Ia acetate		D	6	14	9.5	7.9
Ib acetate		D	6	40	0.27	270
		G	4	150	0.08	930

[a] G represents gavage, D represents drug diet. [b] 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 semilog paper. [c] The quinine equiv Q is the ratio of the SD_{90} of quinine hydrochloride to the SD_{90} of the test substance under comparable exptl conditions. [d] Structures for het N are given in Table III and Schemes II-IV. [e] X represents 2,5-dimethylpyrrol-1-yl.

Table VI. Parenteral Effects of 2,4-Diamino-6-(heterocyclic)quinazolines against *Plasmodium gallinaceum* in Chicks

No.	Route	Single dose, mg/kg	MST of chicks, days			No. of chicks	
			Treated	Controls	ΔMST[a]	Cured[b]	Toxic[c]
23	Iv	120	14.4	4.0	10.4	0	0
	Iv	60	11.2	4.0	7.2	0	0
	Iv	30	10.6	4.0	6.6	0	0
	Sc	30	10.4	4.0	6.4	0	0
	Sc	15	9.8	4.0	5.8	0	0
	Sc	7.5	7.8	4.0	3.8	0	0
25	Sc	120	20.0	4.0	16.0	1	0
26	Sc	160	18.2	4.0	14.2	0	0
Cycloguanil hydrochloride	Sc	120	22.7	3.6	19.1	1	1
	Sc	60	18.7	3.6	15.1	1	1
	Sc	30	15.3	3.6	11.7	1	0
Ia base	Sc	320	20.0	3.4	16.6	3	0
	Sc	160	18.7	3.4	15.3	2	0
	Sc	80	16.3	3.4	12.9	2	0
	Sc	40	15.5	3.4	12.1	1	0
	Sc	20	10.4	3.4	7.0	0	0
	Sc	10	5.6	3.4	2.2	0	0
Ib acetate	Sc	320	20.0	3.1	16.9	4	0
	Sc	120	20.0	3.1	16.9	4	0
	Sc	80	20.0	3.1	16.9	4	0

[a] ΔMST is the mean survival time (days) of treated chicks (MSTT) minus the mean survival time (days) of control chicks (MSTC). [b] Chicks surviving to 30 days postinfection are termed "cured"; data to establish parasitological cure based on subinoculation are unavailable. [c] Deaths occurring within 48 hr after infection 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 5 animal group.

bacillus plantarum (ATCC 8014) (Table VIII). Details of the exptl procedures employed have been described previously.[1] Data on the antimalarial reference compds pyrimethamine, trimethoprim, cycloguanil hydrochloride, and the 2,4-diaminoquinazolines Ia and b together with aminopterin and methotrexate are included for comparative purposes.

Most of the 2,4-diamino-6-(heterocyclic)quinazolines exhibit moderate to strong inhibitory effects against *Strep. faecalis* R utilizing FA as the substrate (Table VIII). These substances inhibit one or both reduction stages and are competitive with FA. Five quinazolines (**24, 34, 35, 40,** and **47**) produced 50% inhibition at concns of 1–14 ng/ml, and thus were equipotent or more potent than pyrimethamine, trimethoprim, cycloguanil hydrochloride, aminopterin, and the benzylaminoquinazolines Ia and b. With the exception of compds **21** and **34**, the *Strep. faecalis* R inhibition was fairly well reversed by 5-CHO-FAH_4, while the inhibitory effects of **34** and **40** were completely reversed by the substrate 5-CHO-FAH_4, adenosine, and thymidine.

The heterocyclic quinazolines **21, 24, 35, 37,** and **47** caused 50% inhibition of *L. plantarum* at concns ranging from 158 to 315 ng/ml, a level of activity roughly comparable with that shown by pyrimethamine, trimethoprim, cycloguanil hydrochloride, and the quinazolines Ia and b (Table VIII).

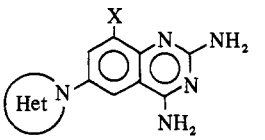
Against the methotrexate- and aminopterin-resistant *Strep. faecalis* A, five compds (**24, 30, 34, 35, 47**) caused 50% inhibition at concns of 70–640 ng/ml utilizing FA as the substrate (Table VIII). These inhibitory concns are comparable with or less than those required for pyrimethamine, trimethoprim, cycloguanil hydrochloride, and Ia and b (150–680 ng/ml). The *Strep. faecalis* A to *Strep. faecalis* R inhibition ratios (31–132) for these compds are relatively low compared with those observed for aminopterin (>20,000) and methotrexate (19,000). This indicates that there is relatively little cross-resistance between these quinazolines and aminopterin or methotrexate utilizing *Strep. faecalis.* Compds **22, 36,** and **44** displayed relatively weak inhibitory effects against all three organisms, which suggests that they may not be folate antagonists at all (Table VIII).

Although heterocyclic quinazolines that exhibit potent inhibitory effects against *Strep. faecalis* R often display strong antimalarial effects (**21, 24, 30, 34, 47**), there are several notable exceptions (**35, 37, 40**) (Tables V *vs.* VIII). Conversely, compd **44**, which is a relatively weak folate antagonist, showed good antimalarial activity. The quinazolines that were active against *T. cruzi* in CEC culture (**21, 34, 35, 40**) were also potent inhibitors of *Strep. faecalis* R, whereas **22**, a relatively poor inhibitor of *Strep. faecalis* R, lacked antitrypanosomal effects. Overall, compds that exhibited strong

Table VII. *In Vitro* Antibacterial Effects of 2,4-Diamino-6-(heterocyclic)quinazolines

	Minimum inhibitory concn, μg/ml					
No.	*Strep. faecalis* MGH-2	*Staph. aureus* UC-76	*Staph. aureus* S18713	*Ps. aeruginosa* 28	*E. coli* Vogel	*S. sonnei* C-10
21	<0.25	2.5	2.5	>25.0	10.0	15.0
23	<0.25	<0.25	<0.25	>25.0	>25.0	>25.0
24	<0.25	1.0	1.5	>25.0	>25.0	>25.0
25	<0.25	<0.25	2.5	>25.0	10.0	20.0
26	<0.25	<0.25	2.5	>25.0	>25.0	>25.0
27	<0.25	<0.25	<0.25	>25.0	2.0	2.5
28	<0.25	<0.25	<0.25	>25.0	>25.0	>25.0
29	<0.25	2.0	2.0	>25.0	>25.0	>25.0
30	<0.25	10.0	15.0	>25.0	>25.0	>25.0
31	<0.25	<0.25	<0.25	>25.0	>25.0	>25.0
34	<0.25	1.0	1.0	>25.0	2.5	15.0
35	<0.25	<0.25	<0.25	>25.0	>25.0	>25.0
36	>25.0	>25.0	>25.0	>25.0	>25.0	>25.0
37	<0.25	15.0	20.0	>25.0	>25.0	>25.0
40	0.5	2.5	2.5	>25.0	>25.0	>25.0
47	<0.25	<0.25	<0.25	>25.0	1.0	1.5

Table VIII. Inhibitory Effects of 2,4-Diamino-6-(heterocyclic)quinazolines against *Strep. faecalis* R, *L. plantarum,* and *Strep. faecalis* A



		Concns, ng/ml, causing 50% inhibition				
		Strep. faecalis R			*L. plantarum*	*Strep. faecalis* A
No.[e]	X	FA[a]	5-CHO-FAH_4[b]	5-CHO-FAH_4 + adenosine + thymidine[c]	None	FA[d]
21	H	22	248		315	1,340
22	H	23,500			>40,000	20,600
24	H	1	>40		158	132
30	H	20	>400		1,220	620
34	H	14	200	>40,000	2,800	640
35	H	4			176	224
36	H	2,540			2,120	>4,000
37	H	28	>400		190	>400
40	H	13	1,340	>40,000	5,600	3,300
44	*f*	12,600	24,800		12,800	15,800
47	H	1	>40		166	70
Pyrimethamine		4	3,100		590	680
Trimethoprim		12	70	>40,000	74	284
Cycloguanil hydrochloride		8	11,400	>400,000	480	560
Aminopterin		2	4	>40,000		>40,000
Methotrexate		0.2	0.6	>40,000	3	3,800
Ia base		6	112	2,400	550	294
Ib base		4	88	28,600	720	150

[a] 0.4 ng/ml of FA. [b] 0.4 ng/ml of 5-CHO-FAH_4. [c] 0.4 ng/ml of 5-CHO-FAH_4 + 10 μg/ml of adenosine + 10 μg/ml of thymidine. [d] 500 ng/ml of FA. [e] Structures for het N are given in Table III and Schemes II–IV. [f] X represents 2,5-dimethylpyrrol-1-yl.

inhibitory effects against *Strep. faecalis* R (**24, 34, 35, 47**, Table VIII) were also potent inhibitors of *Strep. faecalis* MGH-2 and *Staph. aureus* UC-76 and S18713 (Table VII), but activity against *E. coli* and *S. sonnei* was less predictable (**21**, 34, 47 *vs.* **24**, Table VII).

Experimental Section §§,##

5-(Heterocylic)-2-nitrobenzonitriles (IV, 1-10, Table I). Procedure I. A mixt of 5-chloro-2-nitrobenzonitrile (*III*) (11.0 g, 0.06 mole), piperidine (10.2 g, 0.12 mole), and 2-ethoxyethanol (90 ml) was stirred and heated under reflux for 3 hr. A deep red color rapidly developed. The mixt was concd to half vol, and the cryst residue was treated with 300 ml of 2 *N* HCl at 50°. The yellow needles were collected, washed with H_2O, and dried. The product weighed 13.0 g (94%), mp 126-127°. A small analytical sample was recrystd from EtOH to give bright yellow needles of 2-nitro-5-piperidinobenzonitrile **(1)**, mp 127-128°.

Procedure II. A suspension of 7.6 g (0.03 mole) of 2-(3,4-dichlorophenyl)pyrrolidine hydrochloride in 20 ml of H_2O was made basic with 20 ml of 2 *N* NaOH and was extd three times with $CHCl_3$. The combined $CHCl_3$ extracts were washed with H_2O and dried (K_2CO_3). The drying agent was collected, and the filtrate was evapd to dryness *in vacuo*. A mixt of EtOH and C_6H_6 was added to the residue, and the soln was evapd again. A mixt of the residual oil and 2.2 g (0.015 mole) of 5-chloro-2-nitrobenzonitrile (III) in 12 ml of DMSO was stirred at room temp for 20 hr, then at 55-60° for 2 hr, and finally chilled. The bright yellow cryst solid which formed was collected, washed with cold H_2O, and dried to give 3.4 g (67%) of 5-[2-(3,4-dichlorophenyl)-1-pyrrolidinyl]-2-nitrobenzonitrile **(4)**, mp 188-191°.

2-Amino-5-(heterocyclic)benzonitriles (V, 11-20, Table II). Procedure III. *2-Nitro-5-piperidinobenzonitrile* **(1)** (12.4 g, 0.054 mole) was added slowly, with stirring, to a soln of 40.3 g (0.179 mole) of $SnCl_2 \cdot 2H_2O$ in 125 ml of concd HCl while maintaining the temp below 30° by intermittent cooling. The resulting clear brown soln was stirred at room temp for 3 hr and was then added dropwise to a mixt of 135 g of NaOH in H_2O and ice while keeping the temp below 15°. After 1 hr, the colorless solid that sepd was collected, washed with H_2O, and dried. The crude product weighed 10.7 g (98%), mp 89-92°. Crystn from 1:1 CCl_4-petroleum ether(bp 40-60°) (decolorizing charcoal) gave 7.8 g (72%) of 2-amino-5-piperidinobenzonitrile **(11)** as off-white prisms, mp 92-94°.

Procedure IV. 5-(4-Methyl-1-piperazinyl)-2-nitrobenzonitrile **(2)** (13.0 g, 0.053 mole) was added slowly with stirring to a soln of 39.5 g (0.175 mole) of $SnCl_2 \cdot 2H_2O$ in 122 ml of concd HCl. The temp was held below 30° with external cooling. A thick paste formed, and after 3 hr the yellow color had disappeared. The suspension, dild with 300 ml of H_2O, was then added slowly with stirring to 160 g of NaOH in 300 ml of water and crushed ice while maintaining the temp below 10°. A transient clear soln formed, followed by the sepn of fine needles. The alk mixt was extracted with three 250-ml portions of $CHCl_3$, and the combined extracts were dried ($MgSO_4$) and treated with decolorizing charcoal. Volatile materials were removed *in vacuo*, and the residue was crystd from CCl_4 (decolorizing charcoal). The 2-amino-5-(4-methyl-1-piperazinyl)benzonitrile **(12)** was thus obtained as nearly colorless rods, mp 98-100°, yield, 9.6 g (84%).

Procedure V. A hot soln of 5.6 g (0.015 mole) of 5-[2-(3,4-dichlorophenyl)-1-pyrrolidinyl]-2-nitrobenzonitrile **(4)** in 250 ml of glacial HOAc was added slowly to a stirred soln of 16.0 g (0.071 mole) of $SnCl_2 \cdot 2H_2O$ in 118 ml of concd HCl, keeping the temp of the mixt below 30° by means of a water bath. The mixt was stirred for 22 hr at room temp, filtered to remove a small amount of solid, and poured slowly into an iced soln of 300 ml of 50% aqueous NaOH and 400 ml of H_2O. The ppt that formed was collected, washed with H_2O, and dried *in vacuo* at 45° overnight to give 4.5 g of crude product. A soln of the solid in a minimal amount of C_6H_6 was applied on a 4.8 cm × 25 cm column of alumina (Alcoa; F-20 chromatographic) previously equilibrated with C_6H_6. The column was eluted with 200 ml of C_6H_6 and then with EtOAc. That portion of the EtOAc eluant which contained the product as detd by tlc (alumina-EtOAc; R_f 0.7) was evapd to dryness *in vacuo*. The residue was crystd from *i*-PrOH to give 2.8 g (56%) of 2-amino-5-[2-(3,4-dichlorophenyl)-1-pyrrolidinyl]-benzonitrile **(15)**, mp 134-136°.

Compounds **13, 14,** and **16-20** were prepared according to procedure V, but the chromatography step was omitted.

2,4-Diamino-6-(heterocyclic)quinazolines (VI, 21-31, Table III). Procedure VI. 2-Amino-5-piperidinobenzonitrile **(11)** (7.1 g, 0.035 mole) and chloroformamidine hydrochloride[10] (4.4 g, 0.038 mole) were stirred and heated at 140-145° with 40 ml of dry, redistilled diglyme for 2 hr. The mixt was cooled, and H_2O (140 ml) was added. The resulting clear red soln was treated with 38.8 ml of 2 *N* NaOH. The mixt was refrigerated overnight, and the solid was collected, washed with H_2O, and dried. The crude product weighed 6.6 g, mp 230-260°. Recrystn from 250 ml of 50% EtOH (decolorizing charcoal) afforded 3.4 g (40%) of 2,4-diamino-6-piperidinoquinazoline **(21)** as bright yellow needles, mp 292-294°.

Procedure VII. An intimate mixt of 3.7 g (0.0134 mole) of 2-amino-5-(4-phenylpiperidino)benzonitrile **(19)**, 1.7 g (0.0201 mole) of cyanoguanidine, and 1.15 ml (0.0134 mole) of concd HCl was prepared by grinding with a mortar and pestle. The mixt was placed in a round-bottom flask and heated in an oil bath at 100° for 20 min. The temp was then raised to 151° over 25 min, during which time the mixt melted and resolidified. The mixt was maintained at 145-165° for 20 min and cooled. The residue was slurried with hot H_2O, treated with a large excess of aqueous NaOH, collected, washed with H_2O, and dried *in vacuo* at 60° for 20 hr. The crude base weighed 3.9 g, mp 210-220°. The product was slurried in MeOH, 5.4 g (0.0268 mole) of *p*-toluenesulfonic acid hydrate was added, and the soln was treated with decolorizing charcoal and filtered. The filtrate was evapd to dryness *in vacuo*, and the gummy residue was triturated with boiling *i*-PrOH and recrystd from MeCN. The hydrated beige 2,4-diamino-6-(4-phenylpiperidino)quinazoline di-*p*-toluenesulfonate salt thus obtained weighed 2.6 g (28%). The product melted at 151°, resolidified at 190°, and remelted at 273°. *Anal.* ($C_{19}H_{21}N_5 \cdot 2C_7H_8SO_3 \cdot 2H_2O$) C, H, N, H_2O.

A portion (1.9 g) of the above salt was dissolved in 10 ml of MeOH, and the soln was poured into 30 ml of H_2O containing excess NaOH. The ppt was collected, washed successively with 1 *N* NaOH and H_2O, and dried *in vacuo* at 65° for 18 hr. Recrystn from MeOH (decolorizing charcoal) gave 0.4 g of 2,4-diamino-6-(4-phenylpiperidino)quinazoline **(30)** as tiny yellow crystals, mp 255-257° dec.

2,4-Diamino-6-pyrrol-1-ylquinazoline (34). 2,4,6-Triaminoquinazoline **(33)**[7] (3.5 g, 0.02 mole) and 2,5-diethoxytetrahydrofuran (3.2 g, 0.02 mole) were heated under reflux in 20 ml of glacial HOAc for 1 hr. A clear soln formed at once. The mixt was cooled and dild with 60 ml of Et_2O. The cryst ppt was collected, washed with H_2O, and dried (6.7 g). The product was dissolved in 120 ml of H_2O, and the soln was heated to 75° and basified with concd NH_4OH. A gum sepd which then crystd. The mixt was allowed to stand overnight at 0°, and the product was collected, washed with H_2O, and dried. The product weighed 4.1 g, mp 180-190°. This crude material was placed in a Soxhlet extractor and extd with 130 ml of EtOH for 1 hr. The filtrate was treated with decolorizing charcoal and filtered, and the soln was evapd to 60 ml, heated to boiling, and cooled. The pale yellow rods that sepd were collected, recrystd from EtOH (charcoal), and dried *in vacuo* at 60° to give 1.3 g (26%), mp 204-206° (inserted at 200°). *Anal.* ($C_{12}H_{11}N_5 \cdot 0.5C_2H_5OH$) C, H, N. Repeat on a 0.1 mole-scale afforded 6.8 g (30%), mp 203-206°.

2,4-Diamino-6-(2,5-dimethylpyrrol-1-yl)quinazoline (35). A mixt of 2,4,6-triaminoquinazoline **(33)**[7] (1.7 g, 0.01 mole), acetonylacetone (1.1 g, 0.01 mole), 95% EtOH (15 ml), and glacial HOAc (1.2 ml) was heated under reflux for 4 hr. A clear soln formed rapidly. The mixt was cooled, and the product was collected, washed with EtOH, and dried, yield, 1.8 g (73%), mp 211-240°. Recrystn from EtOH (charcoal) afforded 1.0 g (40%) of nearly colorless, long rods, mp 245-247° dec after drying *in vacuo* at 100° for 4 hr. *Anal.* ($C_{14}H_{15}N_5$) C, H, N. Repeat on a 0.03 mole-scale afforded 3.6 g (48%) of product, mp 245-247°.

***N*-(2,4-Diamino-6-quinazolinyl)phthalimide (36).** A mixt of 8.7 g (0.05 mole) of anhydrous 2,4,6-triaminoquinazoline **(33)**,[7] 7.4 g (0.05 mole) of phthalic anhydride, and 175 ml of DMF was heated under reflux for 3 hr. A clear soln formed after 0.5 hr. The mixt was allowed to cool and was poured into 1 l. of 95% EtOH. The mixt was chilled, and the gelatinous ppt was collected, washed with EtOH, and dried. The product was pulverized under Et_2O to remove residual DMF, collected, washed with H_2O-EtOH, and dried *in vacuo* at 100° for 4 hr. The orange product weighed 13.2 g (85%), mp 329-331° dec. *Anal.* ($C_{16}H_{11}N_5O_2 \cdot 0.33H_2O$) C, H, N.

2,4-Diamino-6-(2-isoindolinyl)quinazoline (37). A mixt of 13.2 g (0.05 mole) of α,α'-dibromo-*o*-xylene (Aldrich), 8.8 g (0.05 mole) of 2,4,6-triaminoquinazoline **(33)**,[7] and 10.6 g (0.1 mole) of anhyd Na_2CO_3 in 100 ml of Me_2CO and 50 ml of H_2O was stirred and heated

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

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

under reflux for 5 hr, when tlc (silica–MeOH, EtOAc, Et_3N) indicated complete reaction. The mixt was cooled and dild with H_2O, and the ppt was collected, washed thoroughly with H_2O, and dried *in vacuo* at 60° for 18 hr. The crude product was recrystd twice from MeOH to give 11.0 g (75%) of yellow crystals, mp 295° dec. *Anal.* ($C_{16}H_{15}N_5 \cdot H_2O$) C, H, N; H_2O: calcd, 6.1; found, 5.6.

2,4-Diamino-6-hydrazinoquinazoline (39). 2,4,6-Triaminoquinazoline **(33)**[7] (5.2 g, 0.03 mole) was dissolved in 63 ml of 2 *N* HCl. As the hydrochloride salt began to sep, the mixt was warmed to give a clear soln and then chilled rapidly to 10°. The soln was stirred and diazotized with a soln of 2.2 g of $NaNO_2$ in 10 ml of H_2O. The soln remained clear for 2 min, but then became clouded with a yellow ppt. The mixt was maintained at 0° and was treated with a soln of 14 g of $SnCl_2 \cdot 2H_2O$ in 18.5 ml of 1:1 HCl over a period of 90 min. Stirring was continued at room temp for 24 hr, and the yellow suspension was made alk with a mixt containing 18 g of NaOH and 18 ml of H_2O. A ppt of $Na_2Sn(OH)_6$ formed immediately, but redissolved leaving a finely divided brown ppt. The ppt was collected, dried, and recrystd three times from H_2O to give 2.6 g (42%) of off-white prisms, mp 236–240° dec after drying *in vacuo* at 50° for 4 hr. *Anal.* ($C_8H_{10}N_6 \cdot H_2O$) C, H, N. Repeat on a 0.08-mole scale afforded 8.9 g (54%) of product, mp 234–235° dec.

2,4-Diamino-6-(3,5-dimethylpyrazol-1-yl)quinazoline (40). 2,4-Diamino-6-hydrazinoquinazoline **(39)** (0.6 g, 0.003 mole) was dissolved in 50 ml of 50% EtOH, 0.3 g (0.0027 mole) of acetylacetone was added, and the mixt was heated under reflux for 4 hr. The mixt was concd to 30 ml and chilled overnight. The ppt was collected, recrystd twice from 50% EtOH (decolorizing charcoal), and dried *in vacuo* at 100° for 4 hr to give 0.2 g (26%) of product as short colorless rods, mp 298–300° dec. *Anal.* ($C_{13}H_{14}N_6$) C, H, N. Repeat on a 0.033-mole scale afforded 5.3 g (63%) of product, mp 296–300°.

2,4-Diamino-6,8-dinitroquinazoline (42). A stirred soln of guanidine hydrochloride (9.6 g, 0.1 mole) in 100 ml of warm, Mg-dried EtOH was treated with Na (2.5 g, 0.11 g-atom) in 100 ml of Mg-dried EtOH, and the NaCl that sepd was collected and discarded. The filtrate was added to 22.3 g (0.1 mole) of 3,5-dinitro-*o*-anisonitrile **(41)**,[11] and the red soln was stirred and boiled under reflux for 2 hr. The mixt was cooled, and the brick-red solid was collected and washed successively with EtOH, H_2O, EtOH, and Et_2O. After drying, the product weighed 21.6 g (86%), mp 335–337° dec. The material was recrystd from DMF–H_2O, washed successively with EtOH and Et_2O, and dried to give golden leaflets, mp 336–337° dec. *Anal.* ($C_8H_6N_6O_4 \cdot 0.33H_2O$) C, H, N. Repeat on a 0.15-mole scale afforded 31.2 g (85%) of product, mp 335–337° dec.

2,4,6,8-Tetraaminoquinazoline (43). A suspension of 19.2 g (0.077 mole) of 2,4-diamino-6,8-dinitroquinazoline **(42)** in 400 ml of DMF was hydrogenated with 10% Pd/C. The exothermic hydrogenation proceeded at 55° without external heating. The theoretical amount of hydrogen (11.1 l. at 20°) was taken up in 2 hr. The mixt was filtered with Supercel and charcoal, and the filtrate was evapd to dryness *in vacuo*. The residue was crystd from H_2O (charcoal) and dried *in vacuo* at 100° for 4 hr to give 13.5 g (93%) of pale yellow felted needles, mp 240° dec. *Anal.* ($C_8H_{10}N_6$) C, H, N. Repeat on a 0.12-mole scale afforded 23.2 g (96%), mp 240° dec.

2,4-Diamino-6,8-bis(2,5-dimethylpyrrol-1-yl)quinazoline (44). A mixt of 1.9 g (0.01 mole) of 2,4,6,8-tetraaminoquinazoline **(43)**, 2.3 g (0.02 mole) of acetonylacetone, 20 ml of 96% EtOH, and 2.4 ml of glacial HOAc was heated under reflux for 3 hr. Soln occurred after 0.5 hr. The mixt was allowed to cool and was made basic with a concd NH_4OH–H_2O mixt. The mixt was chilled to 0°, and the product was collected, washed with 50% EtOH, and dried. Crystn from EtOH–H_2O (decolorizing charcoal) gave 1.1 g (30%) of small prisms, mp 334° after drying *in vacuo* at 100° for 4 hr. *Anal.* ($C_{20}H_{22}N_6 \cdot 0.5H_2O$) C, H, N. Repeat on a 0.03-mole scale afforded 5.6 g (53%) of tiny yellow needles, mp 333–334° dec.

2,4-Diamino-6-(aminomethyl)quinazoline (46). 2,4-Diamino-6-quinazolinecarbonitrile **(45)**[7] (5.5 g, 0.03 mole) was dissolved in 200 ml of DMF that had been satd with NH_3 at 15°. The mixt was hydrogenated over Raney Ni at 103 kg/cm² for 3 hr at 70–75°, cooled, and filtered, and the catalyst was washed with hot H_2O. The filtrate and washings were combined and evapd nearly to dryness. The residue was crystd twice from H_2O (decolorizing charcoal) and dried at 100° *in vacuo* for 8 hr to give 3.0 g (53%) of yellow chunky prisms, mp 239–242°. *Anal.* ($C_5H_{11}N_5$) C, H, N. Repeat on a 0.11- and 0.07-mole scale gave 16.2 g (80%), mp 233–246°, and 10.9 g (82%), mp 233–245°, respectively.

2,4-Diamino-6-[(2,5-dimethylpyrrol-1-yl)methyl]quinazoline (47). A mixt of 2,4-diamino-6-(aminomethyl)quinazoline **(46)** (1.9 g, 0.01 mole), acetonylacetone (1.2 g, 0.01 mole), 15 ml of 96% EtOH, and 1.2 ml of glacial HOAc was heated under reflux for 4 hr. A clear soln formed at once, and a trace of granular solid sepd during the reflux period. The mixt was treated with decolorizing charcoal and filtered, and the filtrate was chilled to 0°. The cryst precipitate that sepd was collected, washed with EtOH, and dried. The crude acetate salt (2.8 g) was dissolved in 20 ml of hot EtOH, and the soln was treated with 5 ml of concd NH_4OH and 60 ml of H_2O. After cooling at 0° for 2 hr, the off-white leaflets that sepd were collected, washed with 25% EtOH, and dried. The yield was 1.9 g (71%), mp 221–225°. Recrystn from 50% EtOH (40 ml) gave 1.6 g (60%) of almost colorless leaflets, mp 222–226° after drying *in vacuo* at 100° for 4 hr. *Anal.* ($C_{15}H_{17}N_5$) C, H, N. Repeat on a 0.02-mole scale afforded 3.7 g (69%), mp 222–226°.

2-(3,4-Dichlorophenyl)-1-pyrroline. Under a steady flow of N_2, a soln of 200 g (0.886 mole) of 4-bromo-1,2-dichlorobenzene in 500 ml of Et_2O was added slowly to a stirring mixt of 21.4 g (0.882 g-atom) of Mg turnings and a cryst of I_2 in 75 ml of Et_2O. After the addn was complete, the mixt was stirred with gentle heating for 1 hr. A soln of 91.7 g (0.886 mole) of 4-chlorobutyronitrile in 300 ml of Et_2O was added slowly to the 3,4-dichlorophenylmagnesium bromide. The mixt was stirred 0.5 hr and then the Et_2O was removed by distn. The vol of the reaction mixt was kept constant by the continuous addition of xylene. When the temp of the mixt reached 137°, distn was discontinued and the mixt was heated under reflux for 3 hr and allowed to cool to room temp overnight. To the stirred mixt was added dropwise 25 ml of a saturated NH_4Cl soln. The mixt was filtered, and the filter cake was washed with 300 ml of H_2O and 200 ml of xylene. The filtrate and washes were combined, and the layers sepd. The xylene layer was washed twice with H_2O and then with 200 ml of concd HCl dild with an equal vol of H_2O. The acid extract was sepd and chilled to afford 61.9 g of the crude product as a hydrochloride salt. This was heated with 1200 ml of a boiling mixt of *i*-PrOH and EtOH (2:3). The mixt was filtered hot to give 31.4 g of solid. The cooled filtrate afforded an additional 13.6 g of material. The filtrate was treated with charcoal and evapd to one-third the original vol to give an additional 6.0 g. The three crops were combined and dissolved in hot H_2O. The soln was poured into iced dil NH_4OH to ppt the product as the base. The material was collected, washed with H_2O, and dried to give 42.5 g (22.3%) of the desired product, mp 110–113° and R_f (alumina–C_6H_6) 0.4. *Anal.* ($C_{10}H_9Cl_2N$) C, H, N.

2-(3,4-Dichlorophenyl)pyrrolidine Monohydrochloride. A mixt of 10.7 g (0.05 mole) of 2-(3,4-dichlorophenyl)-1-pyrroline in 3 ml of glacial HOAc and 70 ml of MeOH was hydrogenated over 0.5 g of 5% Pt/C at room temp under an initial pressure of 3.52 kg/cm² for 1.3 hr and then filtered. The filtrate was evapd to dryness *in vacuo*, and the residue was dissolved in 500 ml of Et_2O and 100 ml of 1 *N* NaOH. The Et_2O layer was sepd, washed with H_2O, dried over anhyd K_2CO_3, and filtered. Ten ml of a 25% soln of HCl in *i*-PrOH was added to the filtrate. The solid that formed was collected and recrystd from *i*-PrOH to give 6.9 g (55%) of the product as the hydrochloride salt, mp 179–181°. *Anal.* ($C_{10}H_{11}Cl_2N \cdot HCl$) C, H, N.

The reaction was repeated with 43.2 g (0.20 mole) of the pyrroline and worked up in an identical manner to give a total of 32.9 g (71%) of the product, mp 179–181°.

2-(*p*-Chlorophenyl)-1-pyrroline. To a stirred mixt of 24.3 g (1.0 g-atom) of Mg turnings and a crystal of I_2 in 75 ml of anhydrous Et_2O was added dropwise a soln of 191.5 g (1.0 mole) of 4-bromo-1-chlorobenzene in 1 l. of Et_2O. After the addition was complete, the mixt was stirred 0.5 hr. A soln of 103.6 g (1.0 mole) of *p*-chlorobutyronitrile in 100 ml of Et_2O was added dropwise to the (*p*-chlorophenyl)-magnesium bromide and the mixt was stirred under reflux for 1 hr. Then, the reflux condenser was reversed, and the Et_2O was allowed to distill off, keeping the vol constant by the addition of xylene. When the temp of the mixt reached 135°, the mixt was heated under reflux for 2 hr and allowed to cool overnight. To the stirred mixt was added dropwise 130 ml of saturated NH_4Cl soln. The mixt was filtered, and the filter cake was washed with xylene and H_2O. The filtrate and washes were combined, and the layers sepd. The H_2O layer was extd with xylene. The xylene fractions were combined, washed with H_2O, dried over anhyd K_2CO_3 in the presence of decolorizing charcoal, filtered through Supercel, and evapd to dryness *in vacuo*. The residue was recrystd from petroleum ether (bp 40–60°) to give 72.6 g (40%) of the product, mp 64–66°. The product was not analyzed but was used directly in the next step.

2-(*p*-Chlorophenyl)pyrrolidine. A mixt of 72.5 g (0.403 mole) of 2-(*p*-chlorophenyl)-1-pyrroline and 2 g of 5% Pt/C in 350 ml of toluene was hydrogenated under an initial pressure of 3.55 kg/cm² and an average temp of 28° for 21.8 hr. An additional gram of 5% Pt/C was added, and hydrogenation was continued for 23.1 hr. The total decrease in pressure was 2.04 kg/cm², 90% of theoretical. The reaction mixt was filtered, and the solvent was removed *in vacuo*.

The residual oil was distilled to yield 66.7 g, bp 130° (7 mm). Vpc demonstrated a 15% contamination with starting material. The hydrogenation was repeated using 59.1 g of this mixt. After filtration and removal of the toluene, distn gave 2 fractions: 16.2 g (25% yield), bp 144–151° (14 mm) (91% by vpc), and 26.7 g (41% yield), bp 150–151° (14 mm) (97% by vpc). *Anal.* ($C_{10}H_{12}ClN$) C, H, N.

2-(*p*-Chlorophenyl)-3,4,5,6-tetrahydropyridine. Under N_2 a soln of 163 g (0.852 mole) of 1-bromo-4-chlorobenzene in 650 ml of Et_2O was added dropwise to a stirred mixt of 20.7 g (0.852 g-atom) of Mg turnings and a crystal of I_2 in 75 ml of Et_2O. To the (*p*-chlorophenyl)-magnesium bromide was added slowly a soln of 100 g (0.852 mole) of 5-chlorovaleronitrile in 100 ml of Et_2O. After the addition was complete, the Et_2O was removed by distn, keeping the vol of the mixt constant by the addition of xylene. When the temp of the flask reached 135°, the mixt was heated under reflux for 1 hr and then allowed to cool slowly overnight. To the mixt cooled in an ice bath was added 120 ml of a satd soln of NH_4Cl. Additional H_2O and C_6H_6 were added to partially dissolve the thick ppt. The mixt was filtered, and the organic layer was sepd, washed with H_2O, treated with anhyd K_2CO_3 and decolorizing charcoal, filtered, and evapd to dryness *in vacuo*. The residue was distd at 6–7 mm to give 21.0 g (13%) of product, bp 149–151°, indicated to be 96% pure by vpc (lit.[14] reports bp 142–150° (20 mm). *Anal.* ($C_{11}H_{20}ClN$) C, H, N.

2-(*p*-Chlorophenyl)piperidine. A soln of 20.8 g (0.108 mole) of 2-(*p*-chlorophenyl)-3,4,5,6-tetrahydropyridine in 100 ml of glacial HOAc was hydrogenated at room temp over 1 g of 5% Pt/C at an initial pressure of 3.52 kg/cm² for 1.45 hr. The mixt was filtered, and the filtrate evapd to dryness *in vacuo*. The residue was dissolved in a mixt of Et_2O and 1 *N* NaOH. The layers were sepd, and the aqueous layer was extd with additional Et_2O. The Et_2O extracts were combined, washed with H_2O, dried over anhyd Na_2SO_4, and filtered. To the filtrate was added 16 ml of a 25% soln of HCl in *i*-PrOH. The solid that ppd was collected, washed with Et_2O, and recrystd from an EtOH–*i*-PrOH mixt to give 15.4 g (61%) of the desired product as the hydrochloride salt, mp 259–260° (lit.[14] reports mp 259–260°).

2-Methyl-3-phenylpyrrolidine Hydrochloride. To a soln of 44.2 g (0.278 mole) of 2-methyl-3-phenyl-1-pyrroline in 60 ml of EtOH was added, in small portions, 10.8 g (0.278 mole) of $NaBH_4$. The mixt, which initially bubbled and warmed, was stirred overnight and then poured into 350 ml of iced H_2O. The oil that formed was extd into $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhyd $MgSO_4$, filtered, and evapd to dryness *in vacuo*. The residue was distd under 0.2–0.25 mm vacuum at 65–84° to give 30 g of a clear liquid. Vpc of the distillate showed that it contained 53% of the product and 43% of the starting material. A mixt of 29.8 g of the distillate and 1 g of 10% Pt/C in 200 ml of MeOH was hydrogenated under an initial pressure of 3.52 kg/cm² at 27° for 21 hr. The decrease in pressure was 0.28 kg/cm², 61% of the theoretical 0.46 kg/cm². Another gram of Pt/C and 12 ml of glacial HOAc were added, and hydrogenation was continued for 2.4 hr. The temp rose to 35°, and the pressure decreased the required 0.18 kg/cm². The reaction mixt was filtered, and the filtrate was evapd to dryness *in vacuo*. The residue was taken up in a mixt of dil NaOH and Et_2O. The layers were sepd, and the aqueous layer was again extd with Et_2O. The Et_2O extracts were combined, dried over anhyd $MgSO_4$, and filtered. To the filtrate was added 40 ml of a 15% soln of HCl in *i*-PrOH. The ppt was collected, washed with Et_2O, and immediately placed in a desiccator over Drierite. The solid was recrystd from EtOH–Et_2O to give 16.2 g (29%) of 2-methyl-3-phenylpyrrolidine hydrochloride, mp 118–120°. *Anal.* ($C_{11}H_{15}N \cdot HCl$) C, H, N.

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