iments. Their other tests were carried out in the presence of 100 nm of exogenous CoQ_{10} and exhibit a higher antimetabolite activity for the phytyl compared to the farnesyl compound. Our data, however, obtained without adding CoQ_{10}, show a higher antimetabolite activity for the farnesyl than for the phytyl group. This suggests that the improvements in synthesis and purification gave a purer product than that of Catlin, *et al.*,[16] and/or that CoQ_{10} is probably more active in reversing the inhibition caused by the farnesyl than by the phytyl compound.

Our data reveal that NADH-oxidase is more sensitive to structural changes in the 6 substituent than is succinoxidase on the basis of the analogs. This relationship is compatible to the greater sensitivity for coenzymatic activity of NADH-oxidase to members of the coenzyme Q group.[1,23] When we added CoQ_{10} to NADH-oxidase which had been treated with the decyl or the heneicosyl analog, complete reversal of the inhibition was observed. Under the conditions, CoQ_{10} caused 0.33–0.5 reversal of the inhibition of the nonadecyl, farnesyl, and phytyl analogs. In the succinoxidase, the addition of the CoQ_{10} caused only a small reversal of the inhibition due to the decyl, pentadecyl, nonadecyl, and farnesyl analogs.

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Folate Antagonists. 9. 2,4-Diamino-6-[(aralkyl)alkylamino]quinazolines, a Potent Class of Antimetabolites with Prodigious Antimalarial Effects†,‡

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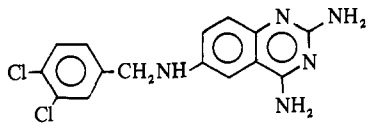
Eighteen 2,4-diamino-6-[(aralkyl)alkylamino]quinazolines (VII) were prepared for antiparasitic and antimetabolite studies. The condensation of 5-chloro-2-nitrobenzonitrile with an *N*-alkylbenzylamine gave 5-[(benzyl)alkylamino]-2-nitrobenzonitriles (V) (25–78%), which were reduced to the corresponding 2-amino-5-[(benzyl)alkylamino]benzonitriles (VI) (48–98%). Cyclization of VI utilizing chloroformamidine·HCl or cyanoguanidine afforded the 2,4-diamino-6-[(benzyl)alkylamino]quinazolines (6–53%). 2,4-Diamino-6-{[ethyl(1-naphthylmethyl)]amino}quinazoline was prepared similarly (14%). Alternatively, reductive alkylation of the requisite 2,4,6-triaminoquinazoline (VIII) with an aliphatic aldehyde over Pt/C yielded various 2,4-diamino-6-(alkylamino)quinazolines (IX) (19–42%), which upon treatment with an α-chlorotoluene derivative afforded VII (21–61%). When administered orally to mice by drug-diet for 6 days, eight of the 2,4-diamino-6-[(aralkyl)alkylamino]quinazolines (VII) were 200–1160 times as potent as quinine·HCl against *Plasmodium berghei* and thus showed suppressive activity comparable with or superior to pyrimethamine (Q = 270), 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]quinazoline (II) (Q = 270), and 2,4-diamino-6-(2-phenyl-1-pyrrolidinyl)quinazoline (III) (Q = 210). Six quinazolines also displayed moderate repository antimalarial effects in mice, and several substances exhibited marked activity orally or parenterally against *P. gallinaceum* in chicks, *P. cynomolgi* and *P. knowlesi* in rhesus monkeys, and *Trypanosoma cruzi* in chick embryo cell culture and in mice. The triaminoquinazolines VII are potent inhibitors of *Streptococcus faecalis* R (*Strep. faecium* var. *durans*) (50% inhibition at 0.2–6 ng/ml), *Strep. faecalis* A (aminopterin-, methotrexate-resistant), and *Lactobacillus plantarum*. Overall structure-activity relationships are discussed.

2,4-Diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (I) and other 2,4-diamino-6-{[aralkyl and (heterocyclic)-methyl]amino}quinazoline antifolates[3,4] display strong antimalarial effects against sensitive and drug-resistant lines of *Plasmodium berghei* in mice, *P. gallinaceum* in chicks, and *P. cynomolgi* and *P. knowlesi* in rhesus monkeys.[3,4] These substances also possess an encouraging degree of activity against *Trypanosoma cruzi* in chick embryo cell cultures and in mice.[3,4] The corresponding 2,4-diamino-6-{[aralkyl

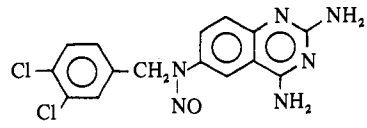
†This is paper 31 of a series on antimalarial drugs. For paper 30, see ref 1.

‡For the previous paper on folate antagonists see ref 2.



I

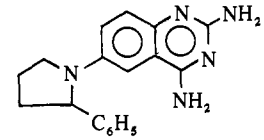
and (heterocyclic)methyl]nitrosamino}quinazolines, exemplified by 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]-quinazoline (II), not only retain the remarkable antiparasitic spectrum that is characteristic of I and its congeners,



II

but usually possess enhanced potency as well.[5-7] Moreover, 2,4-diamino-6-(2-phenyl-1-pyrrolidinyl)quinazoline (III) and related 2,4-diamino-6-(1-pyrrolidinyl or 1-piperidino)-quinazolines,[8,9] which incorporate a tertiary amine function in the saturated heterocyclic ring at position 6, also exhibit more potent antimalarial activity than I.[8,9] We now report the synthesis and biological properties of various 2,4-diamino-6-[(aralkyl)alkylamino]quinazolines (VII), several of which are among the most potent antimalarial drugs known to date in experimental animal systems.

Chemistry. The 2,4-diamino-6-[(aralkyl)alkylamino]-quinazolines (VII) (**1-18**, Tables I, II) described in the present communication were synthesized utilizing the two

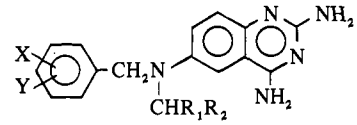


III

routes depicted in Scheme I. In one approach 5-chloro-2-nitrobenzonitrile (IV, Z = H) was condensed with the appropriate *N*-alkylbenzylamine in $EtO(CH_2)_2OH$, $MeO(CH_2)_2OH$, or DMSO to give the corresponding 5-[(benzyl)alkylamino]-2-nitrobenzonitriles (V) (**19-24**, Table III) in 25-78% yield. Reduction of the nitrobenzonitriles (V) with $SnCl_2 \cdot 2H_2O$ in aqueous HCl-HOAc afforded the 2-amino-5-[(benzyl)alkylamino]benzonitriles (VI) (**25-30**, Table IV) (48-98%). Cyclization of the intermediate *o*-aminobenzonitriles (VI) with cyanoguanidine[3] (procedures A and C) or with chloroformamidine hydrochloride[9,10] (procedure B) proceeded in 6-53% yield to give the desired 2,4-diamino-6-[(benzyl)alkylamino]quinazolines (**1-4, 6-10, 14**, Tables I, II). 2,4-Diamino-6-{[ethyl(1-naphthylmethyl)]amino}quinazoline (**17**) was prepared similarly (14%).

Alternatively, reductive alkylation of the requisite 2,4,6-triaminoquinazoline (VIII)[3] with an aliphatic aldehyde over Pt/C yielded the intermediate 2,4-diamino-6-(alkylamino)-quinazolines (IX) (**31-35**, Table V) (19-42%), which upon treatment with the appropriate α-chlorotoluene derivative in the presence of Na_2CO_3 or $NaHCO_3$ afforded the corre-

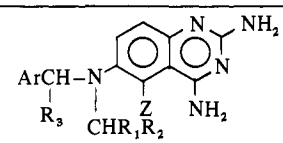
Table I. 2,4-Diamino-6-[(benzyl)alkylamino]quinazolines



No.	X, Y	CHR_1R_2	Mp, °C	Yield purified, %	Purifcn solvent	Route-procedure	Formula	Analyses
1	3,4-Cl_2	CH_3	228-229	37	EtOH	IA	$C_{16}H_{15}Cl_2N_5$	C, H, N
2	3,4-Cl_2	CH_3	289-290	45	EtOH	IB	$C_{16}H_{15}Cl_2N_5 \cdot HCl \cdot 0.5H_2O$	C, H, N, H_2O
3	3,4-Cl_2	CH_3	202-204	44	EtOH	IA	$C_{16}H_{15}Cl_2N_5 \cdot 2CH_4O_3S \cdot 0.5H_2O$[a]	C, H, N, S, H_2O
4	H	CH_3	288-290	53	EtOH	IC	$C_{16}H_{17}N_5 \cdot HCl \cdot H_2O$	C, H, N
5	3,4-Cl_2	C_2H_5	200-202	41	EtOH	IID	$C_{17}H_{17}Cl_2N_5$	C, H, N
6	4-Cl	C_2H_5	203-208	30	MeOH-H_2O	IA	$C_{17}H_{18}ClN_5 \cdot 0.9H_2O$	C, H, N, H_2O
7	3,4-Cl_2	$(CH_2)_2CH_3$	203-204	22	MeCN	IA	$C_{18}H_{19}Cl_2N_5$	C, H, N
8	4-Cl	$(CH_2)_2CH_3$	181-183	25	EtOH	IA	$C_{18}H_{20}ClN_5 \cdot 1.2H_2O$	C, H, N, H_2O
9	4-Cl	$(CH_2)_2CH_3$	200-202	6	HOAc-EtOH	IA	$C_{18}H_{20}ClN_5 \cdot C_2H_4O_2 \cdot 0.5H_2O$[b]	C, H, N, H_2O
10	4-Cl	$CH(CH_3)_2$	191-192	23	EtOH	IA	$C_{18}H_{20}ClN_5$	C, H, N
11	3,4-Cl_2	$(CH_2)_3CH_3$	204-207	21	EtOAc	IID	$C_{19}H_{21}Cl_2N_5$	C, H, N
12	3,4-Cl_2	$(CH_2)_7CH_3$	182-185	25	MeCN	IIE	$C_{23}H_{29}Cl_2N_5$	C, H, Cl, N
13	4-Cl	$(CH_2)_7CH_3$	159-160	24	MeCN	IID	$C_{23}H_{30}ClN_5$	C, H, N

[a] CH_4O_3S represents methanesulfonic acid. [b] $C_2H_4O_2$ represents acetic acid.

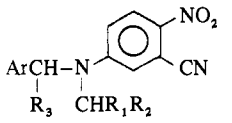
Table II. Other 2,4-Diamino-6-[(aralkyl)alkylamino]quinazolines[a,b]



No.	$ArCHR_3$	CHR_1R_2	Z	Mp, °C	Yield purified, %	Route-procedure	Formula
14	3,4-$Cl_2C_6H_3CH(CH_3)$	CH_3	H	240-241	37	IA	$C_{17}H_{17}Cl_2N_5$
15	3,4-$Cl_2C_6H_3CH_2$	C_2H_5	CH_3	181-183	45	IIE	$C_{18}H_{18}Cl_2N_5$
16	3,4-$Cl_2C_6H_3CH_2$	$(CH_2)_2CH_3$	CH_3	198-199	23	IIE	$C_{19}H_{21}Cl_2N_5$
17	α-Naphthyl-CH_2	C_2H_5	H	242-243	14	IA	$C_{21}H_{21}N_5$
18	$C_6H_5CH_2$	$CH_2C_6H_5$	H	212-214	61	IID	$C_{22}H_{21}N_5$

[a] Compds analyzed for C, H, N. [b] Compds recrystd from EtOH.

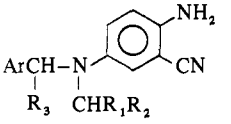
Table III. 5-[(Benzyl)alkylamino]-2-nitrobenzonitriles[a]



No.	$ArCHR_3NCHR_1R_2$	Mp, °C	Yield, purified, %	Purificn solvent	Formula
19	$3,4\text{-}Cl_2C_6H_3CH_2NCH_3$	160-163	78	$MeO(CH_2)_2OH\text{-}H_2O$	$C_{15}H_{11}Cl_2N_3O_2$
20	$C_6H_5CH_2NCH_3$	133-136	77	EtOH	$C_{15}H_{13}N_3O_2$
21	$3,4\text{-}Cl_2C_6H_3CH(CH_3)NCH_3$	140-143	48	Et_2O	$C_{16}H_{13}Cl_2N_3O_2$
22	$4\text{-}ClC_6H_4CH_2NC_2H_5$	145-147	51	$MeO(CH_2)_2OH$	$C_{16}H_{14}ClN_3O_2$
23	$3,4\text{-}Cl_2C_6H_3CH_2N(CH_2)_2CH_3$	143-145	25	$MeO(CH_2)_2OH$	$C_{17}H_{15}Cl_2N_3O_2$
24	$4\text{-}ClC_6H_4CH_2N(CH_2)_2CH_3$	159-161	44	*i*-PrOH	$C_{17}H_{16}ClN_3O_2$

[a] Compds analyzed for C, H, N.

Table IV. 2-Amino-5-[(benzyl)alkylamino]benzonitriles



No.	$ArCHR_3NCHR_1R_2$	Mp, °C	Yield purified, %	Purificn solvent	Formula	Analyses
25	$3,4\text{-}Cl_2C_6H_3CH_2NCH_3$	95-97	83	*i*-PrOH	$C_{15}H_{13}Cl_2N_3$	C, H, N
26	$C_6H_5CH_2NCH_3$	100-102	86	EtOH	$C_{15}H_{15}N_3$	C, H, N
27	$3,4\text{-}Cl_2C_6H_3CH(CH_3)NCH_3$	202-203	79	EtOH	$C_{16}H_{15}Cl_2N_3\cdot HCl$	H, Cl, N; C[a]
28	$4\text{-}ClC_6H_4CH_2NC_2H_5$	215-216	58	EtOH	$C_{16}H_{16}ClN_3\cdot HCl$	C, H, N
29	$3,4\text{-}Cl_2C_6H_3CH_2N(CH_2)_2CH_3$	199-202	98	*i*-PrOH-HCl	$C_{17}H_{17}Cl_2N_3\cdot HCl$	C, H, N
30	$4\text{-}ClC_6H_4CH_2N(CH_2)_2CH_3$	90-95	48	EtOH	$C_{17}H_{18}ClN_3\cdot HCl\cdot H_2O$	H, N, H_2O; C[b]

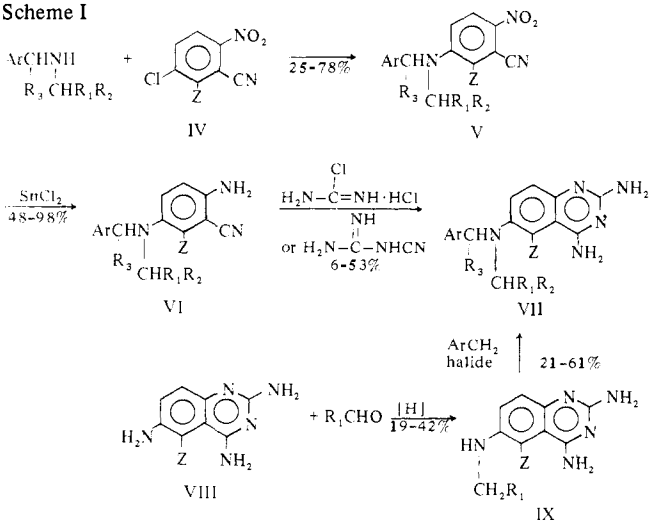
[a] C: calcd, 53.9; found, 53.4. [b] C: calcd, 57.6; found, 57.1.

Table V. 2,4-Diamino-6-(alkylamino)quinazolines

No.	CHR_1R_2	Z	Mp, °C	Yield purified, %	Purificn solvent	Formula	Analyses
31	C_2H_5	H	218-220	27	MeCN	$C_{10}H_{13}N_5\cdot 0.3H_2O$	C,H, N, H_2O
32	C_2H_5	CH_3	222-225	37	EtOH	$C_{11}H_{15}N_5$	C, H, N
33	$(CH_2)_2CH_3$	CH_3	194-197	42	EtOH	$C_{12}H_{17}N_5$	C, H, N
34	$(CH_2)_3CH_3$	H	231-233	19	EtOH	$C_{12}H_{17}N_5$	C, H, N
35	$(CH_2)_7CH_3$	H	167-169	28	EtOH	$C_{16}H_{25}N_5$	C, H, N

sponding 2,4-diamino-6-[(benzyl)alkylamino]quinazolines (VII) (**5**, **11-13**, **15**, **16**, **18**, Tables I, II) in 21-61% yield (procedures D, E). Spectral data (ir, uv, nmr) were in agreement with the structures depicted for each of the 2,4-diamino-6-[(aralkyl)alkylamino]quinazolines.

Scheme I



3,4-Dichloro-α,*N*-dimethylbenzylamine (**36**), which was required as an intermediate for the preparation of **14**, was obtained in 64% yield from 3′,4′-dichloroacetophenone and *N*-methylformamide *via* the Leuckart reaction. *N*-Methyl-3,4-dichlorobenzylamine (**37**) and related benzylamines utilized as intermediates were prepared by reductive alkylation of the requisite benzaldehyde with a primary aliphatic amine over Pt/C (79-86%).

Antimalarial Evaluation. Oral Suppressive Effects in Mice. Fifteen of the 2,4-diamino-6-[(aralkyl)alkylamino]quinazolines (VII) (**2**, **4-7**, **9-18**, Tables I, II) described in the present communication were supplied to Dr. Paul E. Thompson and coworkers of these laboratories for evaluation of their oral suppressive antimalarial effects against a normal drug-sensitive strain (KBG-173) of *P. berghei* in mice utilizing published test procedures.§ Drugs were administered to mice by one of two regimens: D, continuously in the diet for 6 consecutive days; or G, by gavage twice daily for 4 days. Results (Tables VI, VII) are expressed both in terms of the SD_{90} (daily dose required for 90% suppression of the parasitemia in treated mice relative to control mice) and the quinine equivalent *Q* (the ratio of the SD_{90} of quinine

§ For a description of the test methods see ref 4 and 6.

hydrochloride to the SD_{90} of the test substance under comparable experimental conditions). Comparable data for the reference drugs quinine hydrochloride, cycloguanil hydrochloride, pyrimethamine, trimethoprim, 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline acetate (I), 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]quinazoline acetate (II), and 2,4-diamino-6-(2-phenyl-1-pyrrolidinyl)quinazoline (III) are included for comparative purposes (Table VI).

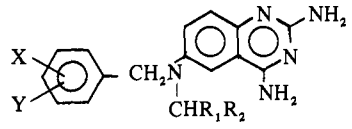
Among ten simple 2,4-diamino-6-[(benzyl)alkylamino]-quinazolines tested (**2**, **4–7**, **9–13**, Table VI), seven compounds (**2**, **4–7**, **9**, **10**) produced 90% suppression of the parasitemia when administered by drug-diet for 6 days at doses of 0.36–0.06 mg/kg per day, and thus ranged from 210 to 1160 times as active as quinine hydrochloride. These exceptional antimalarial substances were also much more potent than the reference drugs cycloguanil hydrochloride, trimethoprim, and I·acetate, and showed activity comparable with or superior to pyrimethamine and the 2,4-diaminoquinazolines II and III.

The size of the N^6-alkyl group plays a dominant role in conferring optimal antimalarial effects. While the introduction of a Me, Et, Pr, or *i*-Pr group at position N^6 of I and congeners increases potency 50- to 275-fold (**2**, **4–7**, **9**, **10**, Table VI), activity drops back within the potency range of the NH series[3] when CHR_1R_2 contains more than 3 carbon atoms (**11–13**, Table VI; **18**, Table VII). The potency-enhancing effect of N^6-alkylation is noteworthy since the alkyl group occupies a position in the quinazoline molecule which relates to key substituents in various FAH_4 coenzymes operating within the folate interconversion cycle.[11] As in the parent NH series,[3] consistently strong antimalarial effects were encountered among both the halobenzyl derivatives (**2**, **5–7**, **9**, **10**) and the unsubstituted benzyl compound **4**.

The oral suppressive antimalarial effects of five other 2,4-diamino-6-[(aralkyl)alkylamino]quinazolines (**14–18**) against *P. berghei* in mice are summarized in Table VII. As in the NH series,[3] substitution of 1-naphthylmethyl for benzyl enabled retention of strong activity and 2,4-diamino-6-{[ethy(1-naphthylmethyl)]amino}quinazoline (**17**) was 200 times as potent (SD_{90} = 0.37 mg/kg per day) as quinine hydrochloride. However, in contradistinction with structure-activity relationships in the NH series,[3] the potency of the 6-[(benzyl)alkylamino] derivatives is markedly reduced by α branching (**14**) or by the introduction of a 5-Me substituent (**15**, **16**) (Table VII).

Parenteral Antimalarial Effects in Mice. 2,4-Diamino-[(3,4-dichlorobenzyl)methylamino]quinazoline (**1**) and

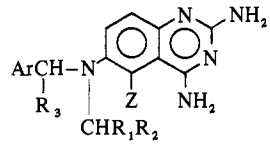
Table VI. Suppressive and Repository Antimalarial Effects of 2,4-Diamino-6-[(benzyl)alkylamino]quinazolines against *Plasmodium berghei* in Mice



				Effects against *P. berghei* in mice							
				Suppressive					Repository		
No.	X, Y	CHR_1R_2	Form	Route[a]	Days	No. of mice	SD_{90}, mg/kg per day[b]	Q[c]	Particle size[d]	Single sc dose, mg/kg[e]	PMW[f]
1	3,4-Cl_2	CH_3	Base						M	400	3.0
2	3,4-Cl_2	CH_3	Hydrochloride	D	6	63	0.16	470	F	400	4.0
3	3,4-Cl_2	CH_3	Dimethane sulfonate						L	200	5.0
4	H	CH_3	Hydrochloride	D	6	56	0.20	370	M	400	4.0
5	3,4-Cl_2	C_2H_5	Base	D	6	21	0.36	210	N	N	N
6	4-Cl	C_2H_5	Base	D	6	42	0.13	570	N	N	N
7	3,4-Cl_2	$(CH_2)_2CH_3$	Base	D	6	21	0.30	250	M	400	T
8	4-Cl	$(CH_2)_2CH_3$	Base						L	400	T
9	4-Cl	$(CH_2)_2CH_3$	Acetate	D	6	35	0.17	440	F	200	T
10	4-Cl	$CH(CH_3)_2$	Base	D	6	21	0.06	1160	N	N	N
11	3,4-Cl_2	$(CH_2)_3CH_3$	Base	D	6	14	3.4	22	F	400	4.0
12	3,4-Cl_2	$(CH_2)_7CH_3$	Base	D	6	14	>15	<5.0	N	N	N
13	4-Cl	$(CH_2)_7CH_3$	Base	D	6	14	34	2.2	N	N	N
Quinine			Hydrochloride	D	6	224	74.5	1.0	N	N	N
				G	4	59	74.0	1.0			
				SC	4	70	50.0	1.0			
Cycloguanil			Hydrochloride	D	6	40	2.1	35	M + L	400	<1.0
				SC	4	28	4.5	11			
Pyrimethamine			Base	D	6	42	0.28	270	N	N	N
				SC	4	28	1.0	50			
Trimethoprim			Base	D	6	21	120	0.6	N	N	N
I			Acetate	D	6	14	9.5	7.9	N	N	N
II			Acetate	D	6	40	0.27	270	F + M	400	2.5
				G	4	150	0.08	930	F + M	400	10.0[g]
III			Base	D	6	28	0.35	210	N	N	N

[a] D, compds were administered continuously in the diet of mice for 6 consecutive days; G, drugs given by gavage twice daily for 4 days as solns or suspensions in H_2O; SC, substances administered subcutaneously twice daily for 4 days as solns or suspensions in 1% aqueous (hydroxyethyl) cellulose. [b] All doses calcd as free base equiv. 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] The particle size range (μ) of the most abundant particles was estimated by gross microscopic examination: fine (F), 0–25 μ; medium (M), 25–75 μ; large (L), >75 μ. [e] Drugs were suspended in 5 ml/kg of benzyl benzoate–castor oil (40:60) (BBCO) and administered sc to groups of 15–25 female albino mice in a single dose of 200 or 400 mg base equiv/kg. Subgroups of five mice were challenged by the ip injection of 15 million *P. berghei* at various intervals, usually 1, 3, 5, 7, and 9 weeks, for susceptibility to malaria. [f] Activity is based on the number of weeks 50% of the mice were protected (PMW). N signifies not tested. T signifies toxic. [g] Suspended in 1.5% Pectin–0.1% Tween 60 in H_2O.

Table VII. Suppressive and Repository Antimalarial Effects of Other 2,4-Diamino-6-[(aralkyl)alkylamino]quinazolines against *Plasmodium berghei* in Mice



				Effects against *Plasmodium berghei* in mice[g]							
				Suppressive					Repository		
No.	$ArCHR_3$	CHR_1R_2	Z	Route[a]	Days	No. of mice	SD_{90}, mg/kg per day[b]	Q[c]	Particle size[d]	Single sc dose, mg/kg[e]	PMW[f]
14	$3,4\text{-}Cl_2C_6H_3CH(CH_3)$	CH_3	H	D	6	21	0.91	82	F + M	400	4.0
15	$3,4\text{-}Cl_2C_6H_3CH_2$	C_2H_5	CH_3	D	6	42	2.4	31	N	N	N
16	$3,4\text{-}Cl_2C_6H_3CH_2$	$(CH_2)_2CH_3$	CH_3	D	6	14	1.7	44	N	N	N
17	α-Naphthyl-CH_2	C_2H_5	H	D	6	21	0.37	200	N	N	N
18	$C_6H_5CH_2$	$CH_2C_6H_5$	H	G	4	20	44	1.7	L	400	<1.0
				SC	4	10	17	2.9			

[a-f] See footnotes *a-f*, Table VI. [g] All compds tested as the free base.

Table VIII. Parenteral Effects of 2,4-Diamino-6-[(3,4-dichlorobenzyl)methylamino]quinazoline (1) and 2,4-Diamino-6-[(*p*-chlorobenzyl)ethylamino]quinazoline (6) against *Plasmodium berghei* in Mice

	ΔMST; C or T[a] after single sc dose, mg/kg									
No.	640	320	160	80	40	20	10	5	2.5	1.25
1	C5	C5	C5	C5	C5	14.9; C3	7.5	2.9	1.5	0.3
		C5	C5	C5	C5	20.9; C2	9.9			
					C5	16.4; C3				
6			T5	C5	C5	C5	13.9	10.9	7.5	2.7
				C5	C5	C5	14.1	10.7	7.9	
						C5	13.4; C1	10.9		
I·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			
II·acetate		C5		C5		22.4; C1				
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				

[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 indicates the number of mice surviving at 60 days postinfection and termed "cured;" data to establish parasitological cure based on subinoculation are unavailable. Each entry at each dose level represents results with a 5 animal group.

2,4-diamino-6-[(*p*-chlorobenzyl)ethylamino]quinazoline (**6**) were also evaluated parenterally against another drug-sensitive strain of *P. berghei* in mice under the auspices of the Walter Reed Army Institute of Research.#,** The drugs were administered in single subcutaneous doses ranging from 1.25 to 640 mg/kg (Table VIII). Compound **1** was curative at doses of 20 through 640 mg/kg, exhibited activity at 10 mg/kg, and enabled a 2.9-day increase in mean survival time at 5 mg/kg. The *p*-chlorophenyl analog (**6**) was toxic for mice at 160 mg/kg, but cured mice at 10–80 mg/kg and showed significant activity at 2.5 and 5 mg/kg. Both compounds were more active parenterally than the reference drugs cycloguanil hydrochloride and the 2,4,6-triaminoquinazolines I and II (Table VIII).

Parenteral Antimalarial Effects in Chicks. Two compounds (**1**, **6**) were tested for suppressive antimalarial effects against *P. gallinaceum* infections in white Leghorn cockerels (Table IX).#,** The drugs were administered to infected chicks in a single sc 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 controls. A compound was arbitrarily considered to be active against malaria if it produced increases in the survival times of treated chicks that were at least 100% greater than the survival times of untreated control animals. 2,4-Diamino-6-[(3,4-dichlorobenzyl)methylamino]quinazoline (**1**) cured 3 of 5 chicks at doses of 160 and 320 mg/kg, and showed activity at doses ranging from 80 mg/kg through 2.5 mg/kg. 2,4-Diamino-6-[(*p*-chlorophenyl)ethylamino]quinazoline (**6**) displayed comparable activity at doses of 2.5–40 mg/kg (Table IX). Both compounds were thus comparable with or superior to the reference drugs cycloguanil hydrochloride and the quinazolines I and II.

Oral Antimalarial Activity in Monkeys. *P. cynomolgi* (B strain) and *P. knowlesi* infections were induced in rhesus monkeys by giving 0.5×10^6 parasitized erythrocytes intravenously. All parasites were taken from donors with ascending parasitemias. Details of the test procedures have been described previously.[3,4,6] Briefly, drug treatment was initiated as soon as daily blood smear examination showed measurable patent infections, usually 5–7 days after inoculation. The quinazolines were administered by stomach tube twice daily as suspensions in 0.1% Tween 80 in 1% hydroxyethyl cellulose for 5 consecutive days. Antimalarial effects were assessed by the examination of thick and thin blood films daily for 48 or 50 days after initiation of treatment.

2,4-Diamino-6-[(3,4-dichlorobenzyl)methylamino]quinazoline hydrochloride (**2**) was tested against patent *P. cynomolgi* infections in 2 monkeys by administering 2 oral 50-

#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 methods, see ref 12.

Table IX. Parenteral Effects of 2,4-Diamino-6-[(3,4-dichlorobenzyl)methylamino]quinazoline (1) and 2,4-Diamino-6-[(*p*-chlorophenyl)ethylamino]quinazoline (6) against *Plasmodium gallinaceum* in Chicks

No.	Single sc dose, mg/kg	MST of chicks, days			No. of chicks	
		Treated	Controls	ΔMST[a]	Cured[b]	Toxic[c]
1	320	28.0	4.0	24.0	3	1
	160	25.0	4.0	21.0	3	0
	80	24.6	4.0	20.6	0	0
	40	19.6	4.0	15.6	0	0
	20	14.6	4.0	10.6	0	0
	10	11.4	4.0	7.4	0	0
	5	10.8	4.0	6.8	0	0
	2.5	10.0	4.0	6.0	0	0
	1.25	5.4	4.0	1.4	0	0
6	40	14.6	4.0	10.6	0	0
	20	13.6	4.0	9.6	0	0
	10	10.0	4.0	6.0	0	0
	5	8.6	4.0	4.6	0	0
	2.5	8.0	4.0	4.0	0	0
	1.25	4.0	4.0	0.0	0	0
Cycloguanil hydrochloride	120	22.7	3.6	19.1	1	1
	60	18.7	3.6	15.1	1	1
	30	15.3	3.6	11.7	1	0
I base	320	20.0	3.4	16.6	3	0
	160	18.7	3.4	15.3	2	0
	80	16.3	3.4	12.9	2	0
	40	15.5	3.4	12.1	1	0
	20	10.4	3.4	7.0	0	0
	10	5.6	3.4	2.2	0	0
II·acetate	320	20.0	3.1	16.9	4	0
	120	20.0	3.1	16.9	4	0
	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.

mg/kg doses per day for 5 days. Both monkeys became negative for asexual forms in 3-4 days, and were apparently cured as indicated by failure to become positive within 14 days after splenectomy on day 36. In like manner, 2,4-diamino-6-(dibenzylamino)quinazoline (**18**) was tested against patent *P. knowlesi* infections in 2 monkeys utilizing the same dosage regimen. Both monkeys became negative for asexual forms in 2-3 days, and were apparently cured as indicated by failure to become positive in 14 days after splenectomy on day 34.

Repository Antimalarial Effects in Mice. Several of the 2,4-diamino-6-[(aralkyl)alkylamino]quinazolines (VII) (**1-4, 7-9, 11, 14, 18**) were evaluated as potential repository antimalarial agents against *P. berghei* in the mouse (Tables VI, VII). As in previous work,††,[14-18] drugs were suspended in 5 ml/kg of benzyl benzoate-castor oil (BBCO, 40:60) and given to groups of 15-25 albino mice in a single subcutaneous dose. Subgroups of treated mice were subsequently challenged with *P. berghei* trophozoites at weekly or biweekly intervals. Assessment of repository action was based on the period of protection against patent infections afforded by a single dose of the drug. Activity is expressed as the number of weeks 50% of the mice were protected (PMW).

Six compounds (**1-4, 11, 14**) exhibited good repository antimalarial activity and protected mice for 3-5 weeks against challenge with *P. berghei* after a single subcutaneous dose of 200 or 400 mg base equiv/kg. Although the drugs were generally tolerated well systemically, they did produce local irritation of moderate intensity at the injection site. The duration of action of these substances compared favorably with the repository activity of 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]quinazoline acetate (II) in the BBCO vehicle, although the latter compound afforded much longer protection when suspended in 1.5% Pectin-0.1% Tween 60 in H_2O.[5,6] However, none of the [(aralkyl)-alkylamino]quinazolines was as promising as the repository antimalarial drugs cycloguanil pamoate,[14,15] acedapsone,[15-17] or 4′,4‴-[*p*-phenylenebis(methylidyneimino-*p*-phenylenesulfonyl)]bisacetanilide (PSBA).[18]

Antitrypanosomal Evaluation. In view of the marked activity of the benzylaminoquinazolines I and II against *T. cruzi* in chick embryo cell (CEC) cultures and in mice,[3-5,7] several representative 2,4-diamino-6-[(aralkyl)alkylamino]-quinazolines (**2, 4, 18**) were evaluated in these test systems. As in earlier work,[3-5,7] a Brazilian strain of *T. cruzi* was utilized for studies both in culture and in mice. Details of the test procedures were reported previously.[3,4,7]

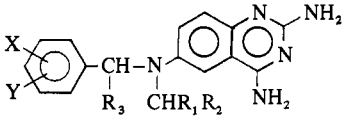
When incubated with *T. cruzi* in CEC cultures for 72 hr, compounds **2** and **4** showed activity at drug concentrations of 0.39-25 μg/ml and 1.6-25 μg/ml, respectively. This activity was reflected by inhibition of extracellular growth, of cell invasion, and of intracellular multiplication. However, drug concentrations above 1.6 μg/ml were cytotoxic for chick embryo cells. Neither compound was more promising than I and II reported previously.[3-5,7] Compound **18** was active only at the highest concentration tested, namely 25 μg/ml.

Compounds **2** and **4** were administered continuously for 14 days in the diet of mice infected with *T. cruzi*. 2,4-Diamino-6-[(3,4-dichlorobenzyl)methylamino]quinazoline (**2**) increased the mean survival time of mice >14 days at drug-diet levels of 0.0078-0.0313%, but did not effect radical cures. Compound **4** lacked appreciable activity at drug-diet levels of 0.0625-0.125%.

Antimetabolite Studies. The prospect that antimetabo-

††This is paper 9 of a series on repository drugs. For paper 8, see ref 13.

Table X. Inhibitory Effects of 2,4-Diamino-6-[(aralkyl)alkylamino]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.	X, Y	R_3	CHR_1R_2	FA[a]	5-CHO-FAH_4[b]	5-CHO-FAH_4 + adenosine + thymidine[c]	None	FA[d]
2	3,4-Cl_2	H	CH_3	0.3	2	1,300	62	13
4	H	H	CH_3	0.2	11	12,800	143	57
6	4-Cl	H	C_2H_5	0.2	>4		50	138
7	3,4-Cl_2	H	$(CH_2)_2CH_3$	0.5	1.5		52	27
8	4-Cl	H	$(CH_2)_2CH_3$	0.5	4		68	28
12	3,4-Cl_2	H	$(CH_2)_7CH_3$	6	>40		156	300
14	3,4-Cl_2	CH_3	CH_3	0.4	>4		132	13
17	2,3- 	H	C_2H_5	0.5			33	14
18	H	H	$CH_2C_6H_5$	1	6	1,300	190	25
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
I base				6	112	2,400	550	294
II 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.

lite studies utilizing bacterial systems might assist in elucidating the biochemical role of the 2,4-diamino-6-[(aralkyl)-alkylamino]quinazolines and help clarify relationships between structure and antimalarial activity stimulated an evaluation of representative compounds (**2**, **4**, **6-8**, **12**, **14**, **17**, **18**) as inhibitors of *Streptococcus faecalis* R (*Strep. faecium* var. *durans*, ATCC 8043), *Strep. faecalis* A (methotrexate-, aminopterin-resistant mutant), and *Lactobacillus plantarum* (ATCC 8014) (Table X). Details of the experimental procedures employed have been described previously.[3] Inhibition data on the antimalarial reference compounds pyrimethamine, trimethoprim, cycloguanil hydrochloride, and the 2,4-diaminoquinazolines I and II, together with aminopterin and methotrexate, are included for comparative purposes.

Each of the 2,4-diamino-6-[(aralkyl)alkylamino]quinazolines exhibited potent inhibitory effects against *Strep. faecalis* R utilizing folic acid (FA) as the substrate (Table X). These substances inhibit one or both reduction stages and are competitive with FA and 5-CHO-FAH_4. Eight quinazolines (**2**, **4**, **6-8**, **14**, **17**, **18**) produced 50% inhibition at concentrations of 0.2-1 ng/ml, and thus were equipotent with or more potent than pyrimethamine, trimethoprim, cycloguanil hydrochloride, aminopterin, and the benzylaminoquinazolines I and II. Moreover, compounds **2**, **4**, and **6** showed activity comparable with methotrexate (50% inhibition at 0.2-0.3 ng/ml). In general, activity against *Strep. faecalis* R was only partly reversed by 5-CHO-FAH_4 (Table X). This suggests that the 2,4-diamino-6-[(aralkyl)alkylamino]quinazolines, like trimethoprim and the 2,4-diamino-6-[(aralkyl)amino]quinazolines,[3] function not only as reductase inhibitors, but also have significant effects either on the folate transport mechanism or elsewhere in the folate cycle. It is interesting to speculate that the known antimalarial effects of 2,4-diamino-6-[(3,4-dichlorobenzyl)-amino]quinazoline (I),[3,4] 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]quinazoline (II),[5,6] 2,4-diamino-6-[(3,4-dichlorobenzyl)methylamino]quinazoline (**1**),[19] trimethoprim, and allied pyrimidines and triazines against cycloguanil- and pyrimethamine-resistant plasmodia may be related to this phenomenon. Moreover, compounds **2**, **4**, and **18** retain some inhibitory effects against *Strep. faecalis* R even in the presence of 5-CHO-FAH_4 plus adenosine plus thymidine (Table X), which suggests that these substances also exert some activity outside the folate cycle.

The nine compounds (**2**, **4**, **6-8**, **12**, **14**, **17**, **18**) tested against *L. plantarum* produced 50% inhibition of this organism within the concentration range 33-156 ng/ml (Table X), and thus showed activity comparable with or superior to pyrimethamine, cycloguanil hydrochloride, and the quinazolines I and II. The inhibitory potency of five substances (**2**, **6-8**, **17**) (33-68 ng/ml) was comparable with that of trimethoprim (74 ng/ml), but none was as potent as methotrexate (3 ng/ml).

Against the methotrexate-, aminopterin-resistant mutant *Strep. faecalis* A, each of the nine compounds tested caused 50% inhibition at concentrations of 13-300 ng/ml utilizing 500 ng/ml of FA as the substrate (Table X). These inhibitory concentrations are equal to or less than that required for pyrimethamine, trimethoprim, cycloguanil hydrochloride, or the quinazolines I and II (150-680 ng/ml). The *Strep. faecalis* A to *Strep. faecalis* R inhibition ratios (25-56) for compounds **2**, **7**, **8**, **12**, **14**, **17**, and **18** are relatively low compared with those observed for aminopterin (>20,000) or methotrexate (19,000). This indicates that there is relatively little cross resistance between these *N*-alkylquinazolines and aminopterin or methotrexate utilizing *Strep. faecalis* (Table X).

Although 2,4-diamino-6-[(aralkyl)alkylamino]quinazolines that exhibit potent inhibitory effects against *Strep. faecalis* R usually display strong antimalarial effects (**2**, **4**, **6-8**, **14**, **17**), there were two notable exceptions (**12**, **18**). Inhibitory effects against *L. plantarum* and *Strep. faecalis* A were also unpredictive. It is concluded that antimetabolite studies

utilizing *Strep. faecalis* R, *Strep. faecalis* A, and *L. plantarum* do not afford a reliable basis for predicting the relative magnitude of antimalarial effects.

Toxicological Studies. Previous preclinical toxicity studies on 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]-quinazoline (II)[5,6] disclosed that adrenal cortical degeneration was a prominent feature of intolerance when rats, dogs, and monkeys were treated over a 3-month period. Furthermore, female rats given single toxic doses of the compound displayed the same anatomical lesions. Therefore, two of the 2,4-diamino-6-[(benzyl)alkylamino]quinazolines (**2**, **4**) described in the present communication were subjected to an acute toxicity study in female rats, followed by microscopic examination of the adrenal glands.[20] Each compound was pulverized thoroughly, suspended at a concentration of 10% in acacia, and administered by gavage in a single dose to groups of five rats at two dose levels known to be in the range of the LD_{50} value for II, namely 317 mg/kg and 502 mg/kg. Among the animals treated with **2**, 3 of 5 survived for 14 days at the 317 mg/kg dose, while none survived at 502 mg/kg. Rats treated with 4 died within 14 days at both doses. Nonsurvivors and survivors to 14 days were autopsied and the adrenal glands were examined histologically. No evidence of adrenal degeneration was observed.[20] The results of preliminary toxicity studies with these and related quinazolines suggest that adrenal degeneration is not an inherent liability of the 2,4-diaminoquinazoline nucleus, but instead is associated with the *N*-nitroso function.

Experimental Section‡‡

2,4-Diamino-6-[(aralkyl)alkylamino]quinazolines (VII) (1-18, Tables I, II). Route I, Procedure A. An intimate mixt of 17.5 g (0.051 mole) of 2-amino-5-[(3,4-dichlorobenzyl)methylamino]-benzonitrile·HCl (prepd by treatment of an EtOH-*i*-PrOH soln of 25 with HCl and concn to dryness) and 4.3 g (0.051 mole) of cyanoguanidine was heated at 160–185° for 15 min, while melting and resolidification occurred. After cooling, the product was washed from the flask with MeOH and digested with 300 ml of hot 1 *N* NaOH. The mixt was chilled, and the ppt was collected and crystd from EtOH to give 2,4-diamino-6-[(3,4-dichlorobenzyl)methylamino]-quinazoline (**1**) as yellow cryst: mp 228–229°.

A soln of 1.0 g (0.0029 mole) of 1 in a MeOH-Me_2CO mixt was treated with 0.58 g (0.006 mole) of $MeSO_3H$. After removal of the solvents on a rotary evaporator, the residue was crystd from EtOH to furnish 0.7 g of the $MeSO_3H$ salt (3) as a pale yellow solid: mp 202–204°.

Route I, Procedure B. A mixt of 6.0 g (0.0195 mole) of 2-amino-5-[(3,4-dichlorobenzyl)methylamino]benzonitrile (25) and 2.5 g (0.0215 mole) of chloroformamidine·HCl[10] in 20 ml of $[MeO(CH_2)_2]_2O$ was heated for 1 hr at 145–160°. After cooling, the mixt was dild with 60 ml of Et_2O, and the ppt was collected and crystd from EtOH to give 3.0 g (45%) of 2,4-diamino-6-[(3,4-dichlorobenzyl)methylamino]quinazoline·HCl·0.5H_2O (2) as yellow needles: mp 289–290°.

Route I, Procedure C. A mixt of 9.5 g (0.040 mole) of 2-amino-5-(benzylmethylamino)benzonitrile (26), 3.4 g (0.040 mole) of cyanoguanidine, and 20 ml of 2 *N* HCl was heated for 9 hr at 100° in a sealed tube. After cooling, the ppt was collected by filtration and was crystd from EtOH to give 3.8 g (53%) of 2,4-diamino-6-[(benzyl)methylamino]quinazoline·HCl·H_2O (4) as yellow rods: mp 288–290°.

Route II, Procedure D. A mixt of 3.0 g (0.015 mole) of 2,4-diamino-6-(ethylamino)quinazoline (31), 3.0 g (0.015 mole) of α,3,4-trichlorotoluene, and 1.6 g (0.015 mole) of Na_2CO_3 in 50 ml of 50% aqueous Me_2CO was heated under reflux on a steam bath for 3 hr. The cooled reaction mixt was dild with H_2O and extd with $CHCl_3$. After washing with dil NaOH and H_2O, the combined exts were dried (K_2CO_3) and concd to dryness. Recrystn twice from EtOH gave 2.2 g (41%) of 2,4-diamino-6-[(3,4-dichlorobenzyl)ethylamino]quinazoline (5) as yellow cryst: mp 200–202°.

Compd 18 was obtained by filtration following dilution of the reaction mixt with H_2O and trituration with petr ether (bp 40–60°).

Route II, Procedure E. A mixt of 2.9 g (0.010 mole) of 2,4-diamino-6-(octylamino)quinazoline (35), 2.2 g (0.011 mole) of α,3,4-trichlorotoluene, and 0.9 g (0.011 mole) of $NaHCO_3$ in 70 ml of 50% Me_2CO was heated under reflux for 2 hr when tlc (silica, EtOAc–MeOH–Et_3N) showed incomplete reaction. An addnl 0.5 g of α,3,4-trichlorotoluene was added, and heating was continued for 3 hr. After cooling, the mixt was dild with H_2O, and the ppt was collected and stirred into a mixt of MeOH (100 ml) and 2 *N* NaOH (15 ml). The mixt was dild with H_2O, and the brown ppt was collected and dried. Treatment with charcoal in EtOH followed by 2 crystns from MeCN gave 1.1 g (25%) of 2,4-diamino-6-[(3,4-dichlorobenzyl)octylamino]quinazoline (**12**) as yellow cryst: mp 182–185°.

5-[(Benzyl)alkylamino]-2-nitrobenzonitriles (V) (19-24, Table III). 5-[(3,4-Dichlorobenzyl)methylamino]-2-nitrobenzonitrile (19). A soln of 80.8 g (0.425 mole) of 3,4-dichloro-*N*-methylbenzylamine, 77.6 g (0.425 mole) of 5-chloro-2-nitrobenzonitrile, and 43.0 g (0.425 mole) of Et_3N in 750 ml of $EtO(CH_2)_2OH$ was heated and stirred on a steam bath for 30 hr. After cooling to 5°, the ppt was collected and was washed with EtOH to produce 100 g (78%) of yellow cryst, mp 151–156°, suitable for use as an intermediate. Recrystn from $MeO(CH_2)_2OH$–H_2O raised the mp to 160–163°.

5-[(Benzyl)methylamino]-2-nitrobenzonitrile (20). A soln of 3.6 g (0.020 mole) of 5-chloro-2-nitrobenzonitrile and 4.8 g (0.040 mole) of *N*-methylbenzylamine in 30 ml of $EtO(CH_2)_2OH$ was heated under reflux for 4 hr. The solvent was removed on a rotary evaporator, and the residue was washed with warm 2 *N* HCl and recrystd from EtOH to give 4.1 g of yellow solid: mp 133–136°.

Intermediates 22–24 were prepd in an analogous manner using $MeO(CH_2)_2OH$ as solvent, 3 moles of the respective substituted benzylamine for each mole of 5-chloro-2-nitrobenzonitrile, and heating for 24 hr.

5-[(3,4-Dichloro-α-methylbenzyl)methylamino]-2-nitrobenzonitrile (21). A soln of 37.5 g (0.156 mole) of 3,4-dichloro-α,*N*-dimethylbenzylamine·HCl (36) in H_2O was treated with excess NaOH, and the resulting mixt was extd with Et_2O. The combined exts were washed with H_2C, dried (K_2CO_3), and concd *in vacuo* to a syrup. 5-Chloro-2-nitrobenzonitrile (14.0 g, 0.076 mole) and 75 ml of DMSO were added, and the mixt was heated at 155° for 2.5 hr. After cooling, the soln was poured into H_2O and extd with Et_2O. The exts were washed with H_2O, dried (K_2CO_3), and concd, and the residue was crystd from Et_2O, mp 140–143°.

5-[(*p*-Chlorobenzyl)isopropylamino]-2-nitrobenzonitrile and **5-[ethyl(1-naphthylmethyl)amino]-2-nitrobenzonitrile** were prepd in the same manner from 5-chloro-2-nitrobenzonitrile and 4-chloro-*N*-isopropylbenzylamine or *N*-ethyl-1-naphthylamine in DMSO, but were used directly without characterization.

2-Amino-5-[(benzyl)alkylamino]benzonitriles (VI) (25-30, Table IV). 2-Amino-5-[(3,4-dichlorobenzyl)methylamino]benzonitrile (25). A soln of 19.1 g (0.057 mole) of 5-[(3,4-dichlorobenzyl)methylamino]-2-nitrobenzonitrile (19) in 230 ml of boiling HOAc was poured slowly into a chilled soln of 42.3 g (0.19 mole) of $SnCl_2·2H_2O$ in 130 ml of concd HCl and 570 ml of HOAc, and the mixt was stirred at 25° for 18 hr. After cooling to 15°, the ppt was collected and stirred into 200 ml of 2 *N* NaOH contg 20 ml of MeOH. Filtration followed by drying gave 14.5 g (83%) of material (mp 94–96°) suitable for use as an intermediate. Recrystn from *i*-PrOH raised the mp to 95–97°.

Compds **26**, **29**, 2-amino-5-[(*p*-chlorobenzyl)isopropylamino]-benzonitrile, and 2-amino-5-[ethyl(1-naphthylmethyl)amino]benzonitrile were obtained similarly on portionwise addn of the respective nitro compds as solids to the $SnCl_2$ soln with sufficient cooling to hold the temp below 30°. The latter 2 compds were used as intermediates without characterization.

2-Amino-5-[(*p*-chlorobenzyl)ethylamino]benzonitrile (28). 5-[(*p*-Chlorobenzyl)ethylamino]-2-nitrobenzonitrile (22) (8.0 g, 0.025 mole) was added portionwise over 15 min to a soln of 22.5 g (0.10 mole) of $SnCl_2·2H_2O$ while the temp was maintained at 25–30° with occasional cooling. After stirring for 18 hr at 25°, the ppt was collected, washed with H_2O, and stirred into excess dil NaOH. The mixt was extd with $CHCl_3$, and the combined exts were washed with 1 *N* NaOH and H_2O and dried (K_2CO_3). Concn and treatment of the residue with *i*-PrOH–HCl followed by crystn from EtOH–Et_2O and EtOH gave 4.7 g of colorless cryst: mp 215–216°.

2-Amino-5-[(3,4-dichloro-α-methylbenzyl)methylamino]benzonitrile (27) and **2-amino-5-[(*p*-chlorobenzyl)propylamino]benzonitrile (30)** were prepd similarly from 5-[(3,4-dichloro-α-methylbenzyl)methylamino]-2-nitrobenzonitrile (21) and 5-[(*p*-chloro-

‡‡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.

benzyl)propylamino]-2-nitrobenzonitrile (24), respectively, with 24 being added in a hot HOAc soln to the $SnCl_2$.

2,4-Diamino-6-(alkylamino)quinazolines (IX) (31-35, Table V). 2,4-Diamino-6-(ethylamino)-5-methylquinazoline (32). A mixt of 12.5 g (0.050 mole) of 5-methyl-2,4,6-triaminoquinazoline·HOAc,[3] 100 ml of $MeO(CH_2)_2OH$, 2.5 g of MeCHO, and 1 g of 10% Pt/C under an initial H_2 pressure of 3.55 kg/cm² was shaken at 24-26° for 23 hr. After removal of the catalyst, the filtrate was concd to dryness, dissolved in H_2O, and treated with charcoal. Addn of excess NaOH gave a ppt which was crystd from EtOH, mp 222-225°.

The other 6-(alkylamino)quinazolines (31, 33-35) were prepd in the same manner except that no HOAc was present in the redn mixt for 34 and 35.

3,4-Dichloro-α,*N*-dimethylbenzylamine (36). A mixt of 100 g (0.53 mole) of 3',4'-dichloroacetophenone, 124 g (2.1 moles) of *N*-methylformamide, and 50 ml of 90% HCO_2H was heated for 7 hr at 160-205° while H_2O was removed through a short distn head. After cooling and diln with H_2O, the mixt was extd with Et_2O. Concn of the combined exts gave an oil which was treated with 200 ml of concd HCl and heated under reflux for 6 hr. The resulting soln was cooled, dild with 1.2 l. of H_2O, and washed with Et_2O. Excess NaOH was added to the aqueous layer and the mixt was extd with three 500-ml portions of Et_2O. The combined exts were washed with H_2O, dried (K_2CO_3), treated with excess HCl in *i*-PrOH, and concd to dryness. Recrystn from EtOH-Et_2O gave 81 g (64%): mp 213-215°. *Anal.* ($C_9H_{11}Cl_2N$·HCl) C, H, N.

N-Methyl-3,4-dichlorobenzylamine (37). A mixt of 240 g (1.37 moles) of 3,4-dichlorobenzaldehyde and 65 g (2.1 moles) of $MeNH_2$ in 1.2 l. of C_6H_5Me was allowed to stand 18 hr at 25°. $MgSO_4$ (120 g) was added and the mixt was filtered after cooling to room temp. The filtrate was charged with 7 g of 5% Pt/C and hydrogenated under an initial pressure of 3.52 kg/cm². After removal of the catalyst by filtration, the filtrate was distilled to give 217 g (84%) of colorless liquid: bp 119-121° (10 mm), $n^{25}D$ 1.5557. *Anal.* ($C_8H_9Cl_2N$) C, H, N.

The other *N*-alkylbenzylamines[21-25] required as intermediates for the synthesis of the 2,4-diamino-6-(alkylamino)quinazolines prepd *via* route I were obtained in the same manner in yields of 79-86%.

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Metabolism of Diphenidol.† Urinary Products in Humans and Dogs

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Following oral administration of [α-^{14}C]diphenidol (1) to humans and dogs the majority of the radioactive label was detected in urinary excretion within 2-3 days. The products of 1 metabolism, most of which were identified, are similar in the two species. Only 5-10% of unchanged 1 was found in the urine. The predominant metabolite, representing more than 50% of the total radioactivity, was *N*-(4,4-diphenyl-4-hydroxybutyl)-δ-aminovaleric acid. This compound was isolated from dog urine and identified in human specimens; its structure was confirmed by synthesis. Smaller amounts of diphenidol glucuronide were noted in both species. Minor urinary products, indicated by chromatographic comparison with compounds synthesized as potential metabolites, included a phenolic derivative of diphenidol, a lactam derived from the major metabolite, and their glucuronides. Neither the major metabolite nor its lactam afforded diphenidol-like protection against apomorphine-induced emesis in dogs.

In an investigation of the metabolism of diphenidol (1),[1] a potent antiemetic agent in man and animals,[2] chromatograms of urine obtained from humans and dogs after oral administration of the α-^{14}C-labeled compound showed a small amount of unchanged drug, a major, and several minor metabolic products. The major metabolite was characterized following its isolation from dog urine. Identification of the other products was undertaken by chromatographic compar-

†Diphenidol is the generic name for α,α-diphenyl-1-piperidinebutanol hydrochloride.