CH_2Cl_2. It was allowed to warm to room temperature and stirred overnight. The mixture was treated with 50 mL of MeOH, stirred for 1 h, evaporated, treated again, and evaporated to dryness. This residue was taken up in a minimum volume of hot MeOH, treated with EtOAC, and allowed to crystallize to give 1.39 g (75%) of white crystals, mp 189–189.5 °C. Anal. ($C_{10}H_{16}N_2O_3S$) C, H, N.

Registry No. 1, 10463-20-4; 2, 70382-04-6; 3, 93565-13-0; 4, 93565-14-1; 3-nitro-4-hydroxyphenylacetyl chloride, 10463-21-5; 4-methoxy-*N*-methyl-3-nitrobenzeneacetamide, 93565-15-2; 4-methoxy-*N*-methyl-3-aminobenzeneacetamide, 93565-16-3; *N*-[2-methoxy-5-[2-(methylamino)ethyl]phenyl]methanesulfonamide, 93565-17-4; calcium, 7440-70-2.

Folate Antagonists. 21. Synthesis and Antimalarial Properties of 2,4-Diamino-6-(benzylamino)pyrido[3,2-*d*]pyrimidines

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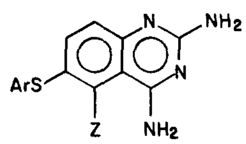
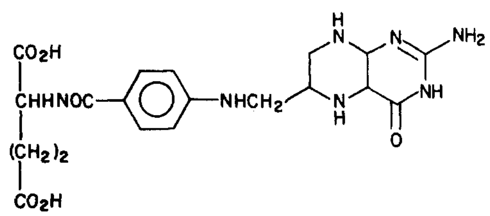
The synthesis and antimalarial activity of a series of 2,4,6-triaminopyrido[3,2-*d*]pyrimidines (4) is described. Several 6-substituted benzylmethylamino analogues were more active against trophozoite induced *Plasmodium berghei* in mice than the corresponding quinazoline analogues. These agents, however, are cross-resistant to other antifolate compounds and are thus of limited potential as human agents.

Our efforts toward the continued exploration of the potent antimalarial activity of the 2,4-diamino-6-(arylthio)quinazolines 1[3] led to the consideration of structures wherein the 2,4-diaminopyrido[3,2-*d*]pyrimidine ring system was substituted for the 2,4-diaminoquinazoline moiety. Such a change might be expected to afford new



1

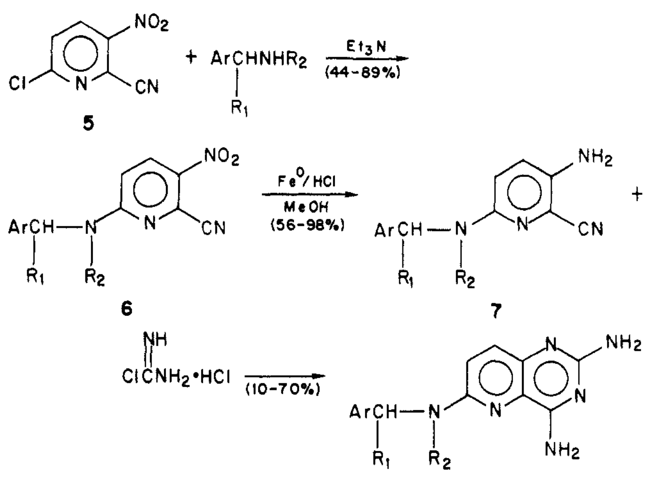
antimetabolites whose architecture, physical properties, and chemical reactivity should more closely resemble the tetrahydrofolate coenzymes 2[4] which are ultimately involved in the biochemistry of the malaria parasite.



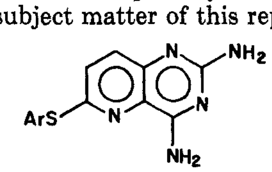
2
(tetrahydrofolic acid)

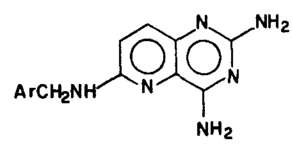
Initial efforts leading to the 2,4-diamino-6-[(arylthio, sulfinyl, and sulfonyl)]pyrido[3,2–*d*]pyrimidines (3)[1] closely related to 1 were disappointing. In contrast, however, the 2,4,6-triaminopyrido[3,2-*d*]pyrimidines (4) exhibited high

Scheme I



antimalarial potency and these compounds constitute the subject matter of this report.





3 4

The synthesis of the requisite 2,4-diamino-6-(benzylamino)pyrido[3,2-*d*]pyrimidines was achieved as shown in Scheme I.

Thus treatment of 6-chloro-3-nitro-2-pyridinecarbonitrile (5) with the appropriate benzylamines in the presence of triethylamine afforded the 6-(benzylamino)-3-nitro-2-pyridinecarbonitriles (6), which were reduced to the corresponding amines 7 with iron in hydrochloric acid (Table I, procedures A and B). Condensation of 7 with chloroformamidine hydrochloride then provided the corresponding 2,4-diamino-6-(benzylamino)pyrido[3,2-*d*]pyrimidines (8, Table II, procedure C).

Oxidation of 9 with peroxytrifluoroacetic acid gave what is presumed to be 6-chloropyrido[3,2-*d*]pyrimidine-2,4-diamine 5-oxide (10) (Scheme II) in 40% yield, which was not characterized but directly condensed with piperidine to give the presumed 6-(1-piperidinyl)pyrido[3,2-*d*]pyri-

(1) This is communication 57 of a series on antimalarial drugs. For paper 56, see: Colbry, N. L.; Elslager, E. F.; Werbel, L. M. *J. Heterocycl. Chem.* **1984**, *21*, 1521. For paper 20, see: Elslager, E. F.; Johnson, J. L.; Werbel, L, M. *J. Med. Chem.* **1983**, *26*, 1753.

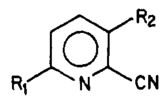
(2) This investigation was supported by U.S. Army Medical Research and Development Command Contracts No. DA49193MD2754 and DADA17-72-C-2077. This is Contribution No. 1698 to the Army Research Program on Malaria.

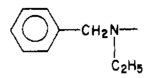
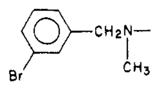
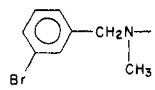
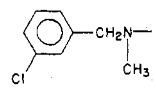
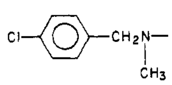
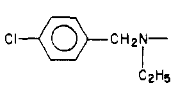
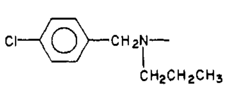
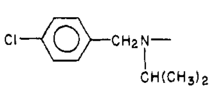
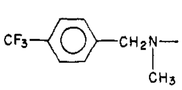
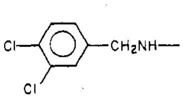
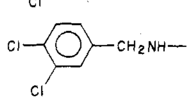
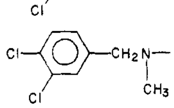
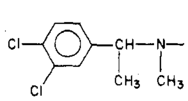
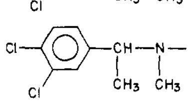
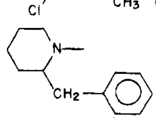
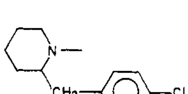
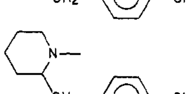
(3) Elslager, E. F.; Jacob, P.; Johnson, J.; Werbel, L. M.; Worth, D. F.; Rane, L. *J. Med. Chem.* **1978**, *21*, 1059.

(4) For discussion and preliminary report of this work, see: Elslager, E. F. *Med. Chem., Proc. Int. Symp. Med. Chem. 4th, 1974* 1974, 227–270.

0022-2623/85/1828-0248$01.50/0

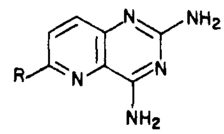
Table I. 6-Amino-3-(amino,nitro)-2-pyridinecarbonitriles

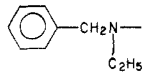
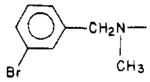
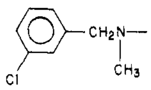
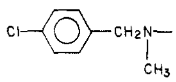
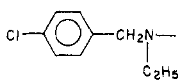
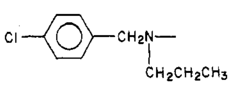
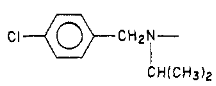
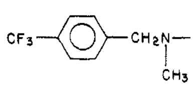
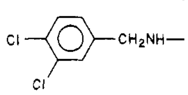
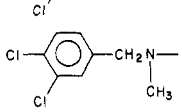
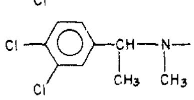
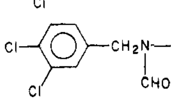
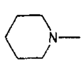
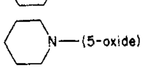
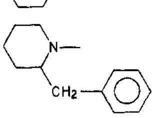
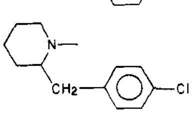


no.	R_1	R_2	mp, °C	yield purified, %	purification solvent	procedure	formula	anal.
6a		NO_2	119.5–121	80	EtOH	J	$C_{15}H_{14}N_4O_2$	CHN
7a		NH_2	oil	88		K	$C_{15}H_{16}N_4$	b
6b		NO_2	147–148	81	EtOH	J	$C_{14}H_{11}BrN_4O_2$	CHN
7b		NH_2	128–130	70	95% EtOH	K	$C_{14}H_{13}BrN_4$	CHN
6c		NO_2	133.5–135	88	EtOH	J	$C_{14}H_{11}ClN_4O_2$	CHN
7c		NH_2	113–115	98	H_2O	K	$C_{14}H_{13}ClN_4$	b
6d		NO_2	95–96	67	EtOH[a]	J	$C_{14}H_{11}ClN_4O_2$	
7d		NH_2	103–104	82	H_2O	K	$C_{14}H_{13}ClN_4$	CHN
6e		NO_2	121–127	89	H_2O	J	$C_{15}H_{13}ClN_4O_2$	b
7e		NH_2	95–97	56	95% EtOH	K	$C_{15}H_{15}ClN_4$	CHN
6f		NO_2	112–114	78	95% EtOh	J	$C_{16}H_{15}ClN_4O_2$	CHN
7f		NH_2	103–105	63	95% EtOH	K	$C_{16}H_{17}ClN_4$	b
6g		NO_2	135–137	45	EtOH	J	$C_{16}H_{15}ClN_4O_2$	CHN
7g		NH_2	oil	97		K	$C_{16}H_{17}ClN_4$	b
6h		NO_2	105–106	68	95% EtOH	J	$C_{15}H_{11}F_3N_4O_2$	CHN
7h		NH_2	118.5–120	67	95% EtOH	K	$C_{15}H_{13}F_3N_4$	CHN
6i		NO_2	179–180	44	95% EtOH	J	$C_{13}H_8Cl_2N_4O_2$	CHN
7i		NH_2	119.5–121	68	benzene–hexane	K	$C_{13}H_{10}Cl_2N_4$	CHNCl
6j		NO_2	122–126	83	EtOH–EtOAc	J	$C_{14}H_{10}Cl_2N_4O$	CHN
7j		NH_2	128–132	70	95% EtOH	K	$C_{14}H_{12}Cl_2N_4$	b
6k		NO_2	95–100	63	MeOH	J	$C_{15}H_{12}Cl_2N_4O_2$	CHN
7k		NH_2	118–120	63	EtOH	K	$C_{15}H_{14}Cl_2N_4$	CHN
6l		NO_2	113.5–115	57	95% EtOH	J	$C_{18}H_{18}N_4O_2$	CHN
7l		NH_2	164–165	72	EtOH–H_2O	K	$C_{18}H_{20}N_4$	b
6m		NO_2	168–169	60	EtOH	J	$C_{18}H_{17}ClN_4O_2$	CHN
7m		NH_2	162–163	68	95% EtOH	K	$C_{18}H_{17}ClN_4$	CHN

[a] Triturated with boiling solvent. [b] This material was of sufficient purity for use in further reaction.

Table II. 2,4,6-Triaminopyrido[3,2-*d*]pyrimidines



no.	R	mp, °C	yield purified, %	purification solvent	procedure	formula	anal.
8a		201–203	27	acetone–ethanol	L	$C_{16}H_8N_6$	CHN
8b		242–244	58	ethanol	L	$C_{15}H_{15}BrN_6$	CHN
8c		254–257	51	ethanol	L	$C_{15}H_{15}ClN_6$	CHN
8d		218–220	70	methanol	L	$C_{15}H_{15}ClN_6$	CHN
8e		198–202	59	methanol	L	$C_{16}H_{17}ClN_6$	CHN
8f		204–207	53	ethanol	L	$C_{17}H_{19}ClN_6$	CHN
8g		206–207	10	CH_3CN	L	$C_{17}H_{19}ClN_6 \cdot CH_3CN$	CHN
8h		212–214	53	ethanol	L	$C_{16}H_{15}F_3N_6$	CHN
8i		198–221	35	ethyl acetate[a]–ether	L	$C_{14}H_{12}Cl_2N_6 \cdot 0.18H_2O$	CHN·H_2O
8j		248.5–251.5	30	methanol	L	$C_{15}H_{14}Cl_2N_6$	CHNCl
8k		216–218	43	acetone[a]	L	$C_{16}H_{16}Cl_2N_6$	CHN
8l		218–221	35	95% ethanol	L	$C_{1k}H_{12}Cl_2N_6O$	CHN
8m		235–237	45	water[a]	M	$C_{12}H_{16}N_6$	CHN
8n		267 dec	45	water[a]	N	$C_{12}H_{16}N_6O$	CHN
8o		183–186	14	benzene	L	$C_{19}H_{22}N_6 \cdot 0.33H_2O$	CHN·H_2O
8p		120–124	21	95% ethanol	L	$C_{19}H_{21}ClN_6 \cdot C_2H_5OH \cdot 0.2H_2O$	CHN·H_2O

[a] Triturated with boiling solvent.

midine-2,4-diamine 5-oxide (Scheme II).

Direct condensation of amines with 6-chloro-2,4-diaminopyrido[3,2-*d*]pyrimidine (**9**)[5] was successful only with piperidine (Scheme II). Therefore several other substituted piperidine analogues (Table II, compounds **8o,p**) were prepared as indicated in Scheme I.

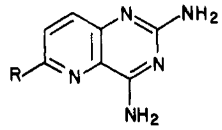
Formylation of compound **8i** (Table II) with formic acid provided the *N*-formyl derivative, compound **8l** (Table II).

Biology. The 2,4-diamino-6-(benzylamino)pyrido[3,2-*d*]pyrimidine **8a–l** and the piperidine analogues **8m–p** were tested against a normal drug-sensitive strain of *Plasmodium berghei* in mice by the parenteral route[6,7] (Table III).

(5) Colbry, N. F.; Elslager, E. F.; Werbel, L. M. *J. Heterocycl. Chem.* **1984**, *21*, 1521.

(6) Osdene, T. S.; Russell, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.

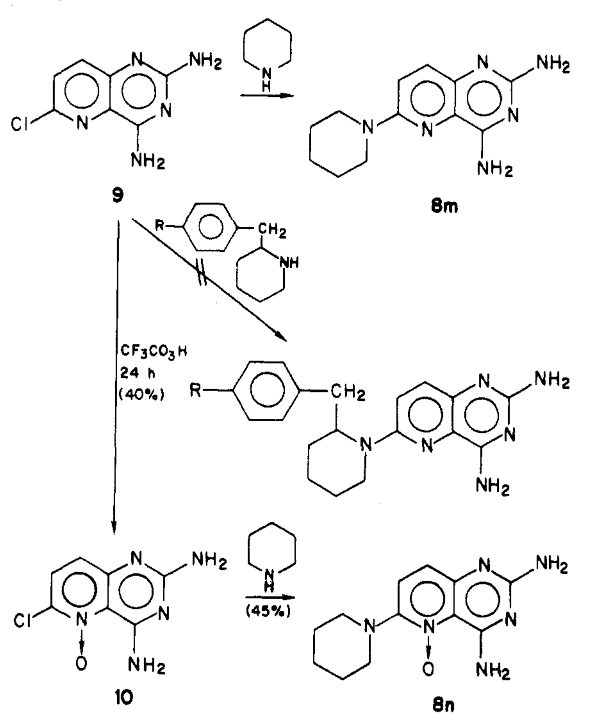
Table III. Parenteral Suppressive Antimalarial Effects of 2,4,6-Triaminopyrido[3,2-d]pyrimidines against Trophozoite-Induced *P. berghei* in Mice



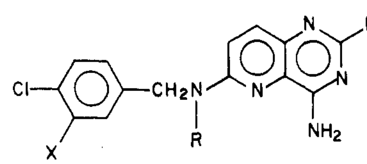
compd	ΔMST; C or T[a] after a dose, mg/kg									
	640	320	160	80	40	20	10	5	2.5	1.25
8a	T10/10	T3/5	T2/10	C5/5	C4/10	9.7				
8b	C9/15	C3/5	C6/15	C1/5	9.8	9.1				
8c	C5/5	C5/5	C5/5	C5/5	C5/5	C3/5				
8d	1.3		1.1		1.1					
8e	1.1		0.9		0.9					
8f	T15/15	T10/10	T14/20	C5/5	21.3	18.0	10.3	8.9	8.1	6.9
8g	T5/5	T8/10	T8/10	T4/10	C11/15	C3/15	11.5	8.5	6.5	3.5
8h	2.5	2.9	C1/5	C4/5	C8/10	8.1				
8i	C7/10	15.3	12.4	4.9	1.8	0.5				
8j		C5/5	C5/5	C5/5	C10/10	C8/10	11.9	9.1	4.3	2.9
8k	3.9		2.3		1.7					
8l	C10/10	C5/10	C10/10	C5/5	C6/15	C4/10	16.3	14.1	5.3	1.9
8m	T5/5		0.4		0.3					
8o		C10/10	C5/5	8.2	4.9	3.0				
8p	C7/10	C2/5	C4/10	9.1	5.1	2.9				
WR-158,302	C5/5	C10/10	C10/10	C10/10	C15/15	C8/15	8.7			
WR-162,882	C5/5	C10/10	C10/10	C10/10	C4/10	8.2	4.3			
cycloguanil hydrochloride	T5	C3; T2	C5	21.6; C2	13.4; Cl	7.9	4.9			
pyrimethamine	C1; T2	C2; T3	C5	C3	C1	7.7	6.1	5.3	4.7	3.1

[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 ranged from 6.1 to 6.3 days. T signifies the number of toxic deaths, occurring on days 2–5 after injection, which are attributed to drug action. Compounds are arbitrarily considered to be "active" when they produce at least a 100% increase in the mean survival time of treated mice. 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 when not indicated otherwise represents results with a five-animal group.

Scheme II

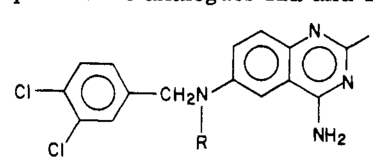


In general, the pyridopyrimidines described showed potent antimalarial activity, although in several cases the results are rather puzzling. Thus, for example, the extremely high activity demonstrated by **8j** is in strange contrast to the inactivity of the monochloro analogues **8d,e**.



8j, X = Cl; R = CH_3
d, X = H; R = CH_3
e, X = H; R = C_2H_5

Moreover, several compounds such as 2,4-diamino-6-[(3,4-dichlorobenzyl)methylamino]pyrido[3,2-*d*]pyrimidine (compound **8j**), *N*-(2,4-diaminopyrido[3,2-*d*]pyrimidin-6-yl)-*N*-(3,4-dichlorobenzyl)formamide (compound **8l**), and 2,4-diamino-6-[(*p*-chlorobenzyl)isopropylamino]pyrido-[3,2-*d*]pyrimidine (compound **8g**) were more active against trophozoite-induced *P. berghei* in mice than the corresponding quinazoline analogues **12a** and **12b**.



12a, R = CH_3, WR-158, 302
b, R = CHO, WR-162, 882

Two members of the 2,4,6-triaminopyrido[3,2-*d*]pyrimidine series, namely, 2,4-diamino-6-[(*p*-chlorobenzyl)-propylamino]pyrido[3,2-*d*]pyrimidine (compound **8f**) and 2,4-diamino-6-[(*m*-bromobenzyl)methylamino]pyrido[3,2-*d*]pyrimidine (compound **8b**) (Table II), have been tested orally against both sensitive and drug-resistant lines of *P. berghei* in mice. The SD_{90} of **8f** for each line was as follows: line P, 0.9 mg/kg; line T, >6.25 mg/kg; line PYR, >6.25 mg/kg; line S, 3.3 mg/kg; and line C, 0.88 mg/kg.

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

These results indicate that **8f** was fully active against the chloroquine-resistant line C, but that there was >13-fold cross-resistance with cycloguanil (T) and pyrimethamine (PYR) and 4-fold cross-resistance with dapsone (S).[8,9] Compound **8b** was also cross-resistant with cycloguanil (4-fold) and pyrimethamine (5-fold), although to a lesser degree. It has been postulated[4] that the lack of cross-resistance of the antimalarial 2,4-diaminoquinazolines might result from prevention of the one-carbon transfer reactions within the folate interconversion cycle. Thus the derivatives of the reduced tetrahydro form of folic acid which involve cyclic structures utilizing the nitrogen at the 5-position are precluded in the deazaquinazoline structures. Formation of such structures would be possible with the current 2,4,6-triaminopyrido[3,2-*d*]pyrimidines which possess a nitrogen at position 5 and thus the observed cross-resistance is in accord with the previous hypothesis. It is concluded that future work on novel folate antagonists as potential antimalarial agents should be oriented toward the synthesis of heterocyclic systems which lack N-5.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are corrected. Satisfactory infrared (Beckman IR-9) and NMR (Bruker WH-90) spectra were obtained for all compounds.

6-Amino-3-nitro-2-pyridinecarbonitriles (6). Procedure A. A solution of 3-bromo-*N*-methylbenzenemethanamine (6.0 g, 0.030 mol), 6-chloro-3-nitro-2-pyridinecarbonitrile (**5**) (5.0 g, 0.027 mol), and Et_3N (3.5 g, 0.03 mol) in 2-ethoxyethanol (50 mL) was heated on a steam bath for 1 h and poured into H_2O. The resulting solid was collected, washed with H_2O, and crystallized from EtOH (600 mL) to give 6-[[(3-bromophenyl)methyl]-methylamino]-3-nitro-2-pyridinecarbonitrile (compound **6b**, Table I) (7.7 g, 81%) as bright yellow crystals, mp 147–148 °C. Anal. ($C_{14}H_{11}BrN_4O_2$) C, H, N. Compounds **6a,c–m** (Table I) were prepared by this method.

3,6-Diamino-2-pyridinecarbonitriles (7). Procedure B. To a suspension of 6-[[(3-bromophenyl)methyl]methylamino]-3-nitro-2-pyridinecarbonitrile (**6b**) (7.6 g, 0.0219 mol) in MeOH (100 mL) and concentrated HCl (20 mL) was added portionwise iron powder (6.0 g, 0.11 mol) at a rate sufficient to maintain gentle reflux. When addition was complete, the mixture was heated under gentle reflux for an additional 1 h and filtered. The filtrate was poured into H_2O and the solid that formed was collected, washed with water, and recrystallized from 95% EtOH to give 3-amino-6-[[(3-bromophenyl)methyl]methylamino]-2-pyridinecarbonitrile (compound **7b**, Table I) (4.9 g, 70%) as brown crystals, mp 128–130 °C. Anal. ($C_{14}H_{13}BrN_4$) C, H, N. Compounds **7c–f,i–k,m** (Table I) were prepared similarly. Compounds **7b,g,h** were made by this method but did not solidify when poured into H_2O. The mixtures were extracted (EtOAc, **7b**, and **7h**, $CHCl_3$, **7g**), and the solvent was removed in vacuo. Compounds **7a** and **7g** were oils that were used directly in the next reaction; **7h** was a solid that was recrystallized before use. Compound **7l** was prepared by this method except that the original iron-containing solid was extracted with hot MeOH, and the combined filtrates were poured into water to give the crude product. Results appear in Table I.

2,4,6-Triaminopyrido[3,2-*d*]pyridines (8). Procedure C. A mixture of 3-amino-6-[[(3-bromophenyl)methyl]methylamino]-2-pyridinecarbonitrile (**7b**) (4.75 g, 0.015 mol), chloroformamidine hydrochloride (3.45 g, 0.030 mol), and dimethyl sulfone (17 g) was heated at 130 °C for 1 h and poured into dilute NaOH. The solid that formed was collected, washed with H_2O, and crystallized from EtOH (700 mL) to give N^6-[(3-bromophenyl)methyl]-N^6-methylpyrido[3,2-*d*]pyrimidine-2,4,6-triamine (**8b**) (3.1 g, 58%) as a yellow solid, mp 242–244 °C. Anal. ($C_{15}H_{15}BrN_6$) C, H, N. Compounds **8a–f** (Table II) were prepared similarly. Compounds **8j,k** were also prepared by this method with the exception that they were heated to 170 °C for 1 h and 125 °C for 1.5 h, respectively. The preparation of compound **8g** utilized diglyme as the solvent and heating to 145 °C for 45 min. The crude reaction product was isolated by extraction into Et_2O, and the product was crystallized from benzene and then from MeCN. Compounds **8h,o,p** involved heating to 150–155 °C for 1 h. The low yields reported represent early attempts in whch difficulty was encountered in workup of the reactions.

***N*-(2,4-Diaminopyrido[3,2-*d*]pyrimidin-6-yl)-*N*-[(3,4-dichlorophenyl)methyl]formamide (Table II, 8l).** A solution of N^6-[(3,4-dichlorophenyl)methyl]pyrido[3,2-*d*]pyrimidine-2,4,6-triamine (**8i**) (2.4 g, 7.2 mmol) in 98% formic acid (30 mL) was heated under reflux for 2 h. The solution was evaporated in vacuo and the residue was extracted with 100 mL of hot H_2O. The solution was poured into excess iced NH_4OH. The solid which formed was collected, washed with H_2O, and dried to give crude **8l** as a cream-colored solid (2.0 g). Crystallization from 95% EtOH gave **8l** (0.9 g, 35%) as tan crystals, mp 218–221 °C.

6-(1-Piperidinyl)pyrido[3,2-*d*]pyrimidine-2,4-diamine (Table II, 8m). A slurry of 6-chloropyrido[3,2-*d*]pyrimidine-2,4-diamine (**9**) (3.0 g, 0.015 mol) and piperidine (30 mL) was heated under reflux for 42 h. The hot mixture was filtered and the filtrate was cooled. The solid which formed was collected, washed successively with a small amount of piperidine, EtOH, and H_2O, and then dried in vacuo to give **8m** (1.7 g, 45.5%) as a bright yellow solid, mp 235–237 °C.

6-(1-Piperidinyl)pyrido[3,2-*d*]pyrimidine-2,4-diamine 5-Oxide (Table II, 8n). An ice-cold mixture of 30% H_2O_2 (6.8 mL, 0.068 mol) in CH_2Cl_2 (200 mL) was treated dropwise with trifluoroacetic anhydride. When addition was complete, 6-chloropyrido[3,2-*d*]pyrimidine-2,4-diamine (**9**) (6.0 g, 0.038 mol) was added and the resulting solution was allowed to stir at room temperature for 24 h. The solution was evaporated by passing a stream of nitrogen over the surface and ice water (100 mL) was added to the residue. The solid that formed was washed with cold water and triturated with boiling Me_2CO to give 6-chloropyrido[3,2-*d*]pyrimidine-2,4-diamine 5-oxide (**10**; Scheme II) (2.56 g, 40% crude yield) as a cream-colored solid, mp 283 °C dec. This solid (1.9 g, 0.009 mol) suspended in piperidine (15 mL) was heated under reflux for 16 h. The resulting slurry was poured into H_2O and the solid that formed was collected. Washing successively with H_2O, Me_2CO, and Et_2O and then drying at 140 °C (0.05 mm) gave **8n** (1.05 g, 45%) as a bright yellow solid, mp 267 °C dec. Anal. C, H, N: calcd, 32.29; found, 32.91.

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Registry No. **5**, 93683-65-9; **6a**, 93683-66-0; **6b**, 93683-67-1; **6c**, 93683-68-2; **6d**, 93683-69-3; **6e**, 93683-70-6; **6f**, 93683-71-7; **6g**, 93683-73-9; **6h**, 93683-73-9; **6i**, 93683-74-0; **6j**, 93683-75-1; **6k**, 93683-76-2; **6l**, 93683-77-3; **6m**, 93683-78-4; **7a**, 93683-79-5; **7b**, 93683-80-8; **7c**, 93683-81-9; **7d**, 93683-82-0; **7e**, 93683-83-1; **7f**, 93683-84-2; **7g**, 93683-85-3; **7h**, 93683-86-4; **7i**, 93683-87-5; **7j**, 93683-88-6; **7k**, 93683-89-7; **7l**, 93683-90-0; **7m**, 93714-42-2; **8a**, 93683-91-1; **8b**, 93683-92-2; **8c**, 93683-93-3; **8d**, 93683-94-4; **8e**, 93683-95-5; **8f**, 93683-96-6; **8g**, 93683-97-7; **8h**, 93683-98-8; **8i**, 93683-99-9; **8j**, 93684-00-5; **8k**, 93684-01-6; **8l**, 93684-02-7; **8m**, 93684-03-8; **8n**, 93684-04-9; **8o**, 93684-05-0; **8p**, 93684-06-1; **9**, 93684-07-2; **10**, 93684-08-3; *m*-$BrC_6H_4CH_2NHMe$, 67344-77-8; $PhCH_2NHEt$, 14321-27-8; *m*-$ClC_6H_4CH_2NHMe$, 39191-07-6; *p*-$ClC_6H_4CH_2NHMe$, 104-11-0; *p*-$ClC_6H_4CH_2NHEt$, 69957-83-1; *p*-$ClC_6H_4CH_2NHPr$, 55245-43-7; *p*-$ClC_6H_4CH_2NH$-*i*-Pr, 40066-21-5; *p*-$CF_3C_6H_4CH_2NHMe$, 90390-11-7; 3,4-$Cl_2C_6H_3CH_2NH_2$, 102-49-8; 3,4-$Cl_2C_6H_3CH_2NHMe$, 5635-67-6; 3,4-$Cl_2C_6H_3CH(CH_3)NHMe$, 40023-76-5; $NH{=}C(Cl)NH_2 \cdot HCl$, 29671-92-9; piperidine, 110-89-4; 2-benzylpiperidine, 32838-55-4; 2-[(4-chlorophenyl)methyl]piperidine, 63587-52-0.

(8) Elslager, E. F.; Colbry, N. F.; Werbel, L. M. presented at the Antimalarial Conference, Walter Reed Army Institute of Research, Washington, DC, June 13, 1973.

(9) Elslager, E. F. "Abstracts of Papers"; 8th Great Lakes Regional Meeting of the American Chemical Society, Purdue University, West Lafayette, IN, June 3–5, 1974; American Chemical Society: Washington, DC, 1974; MEDI/ORGN/65.