humidity, and 5% CO_2. Exponentially growing cells (4×10^5 cells/mL) were incubated with test compounds at concentrations of 1, 10, or 100 μm. Cell counts were taken at 24, 48, and 72 h. Cell viability was measured by the trypan blue exclusion technique.[16] Stability of all suspensions was monitored throughout the test period by thin-layer chromatography.

(16) Warren, J. R.; Leatherman, D. L.; Metzger, J. F. *J. Immunol.* **1975**, *115*, 49.

Acknowledgment. This research was supported partly by Grant 903A awarded by the Northeast Louisiana University Research Committee and in part by the Northeast Louisiana School of Pharmacy. Annette Shipp is a Silas M. Burroughs Fellow of the American Foundation for Pharmaceutical Education.

Registry No. **2**, 51-21-8; **3**, 93473-97-3; **4**, 70758-92-8; **5**, 93473-98-4; **6**, 93473-99-5; **7**, 17242-85-2; **9**, 93474-00-1; **11**, 93474-01-2; hexamethyldisilazane, 999-97-3.

N-[2-Hydroxy-5-[2-(methylamino)ethyl]phenyl]methanesulfonamide. A Potent Agonist Which Releases Intracellular Calcium by Activation of α_1-Adrenoceptors

Robert M. DeMarinis,* Patricia Lavanchy, J. Paul Hieble, Kam F. Jim, and William D. Matthews

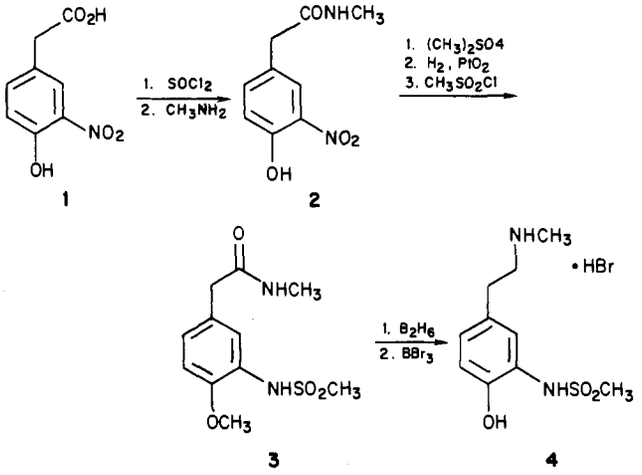
Department of Medicinal Chemistry and Pharmacology, Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101. *Received May 9, 1984*

N-[2-Hydroxy-5-[2-(methylamino)ethyl]phenyl]methanesulfonamide (SK&F 102652) has been prepared and characterized pharmacologically. It is a potent agonist with an EC_{50} of 25 nM at α_1-adrenoceptors as determned in the isolated perfused rabbit ear artery. On the presynaptic α_2-adrenoceptors of the guinea pig atrium it was considerably weaker, demonstrating an EC_{50} for inhibition of neurotransmission of 1200 nM and thus an overall α_1/α_2 selectivity ratio of ≥48. In the vascular smooth muscle of the canine saphenous vein an EC_{100} concentration of this agonist in the presence of zero external Ca^{2+} induced 37.9 ± 1.4% of the maximal contractile response due to this agent while the endogenous ligand norepinephrine evoked only 14.5 ± 0.4% of the maximum. In the presence of low (1 μM) external calcium, this agent produced 78.3 ± 5.3% of maximum while norepinephrine gave 45.3 ± 7.4%. This agent produces α_1-adrenoceptor-mediated contraction primarily by release of intracellular Ca^{2+} and should provide a useful tool for characterizing α_1-receptor subtypes.

In the last several years, it has been amply demonstrated that two distinct types of postsynaptic α-adrenoceptors (α_1, α_2) are present on vascular smooth muscle and that activation of either subtype causes vasoconstriction.[1-3] Evidence has been produced from both in vitro and in vivo experiments to indicate that there is a pharmacological difference in the Ca^{2+} utilization process of smooth muscle after stimulation of α_1- or α_2-adrenoceptors.[4-6] Studies from a number of laboratories have shown that activation of postsynaptic α_2-adrenoceptors causes the influx of extracellular Ca^{2+} across the cell membrane and that it is this translocation of Ca^{2+} that mediates the contractile process.[6-8] On the other hand, activation of postsynaptic α_1-adrenoceptors can induce both extracellular Ca^{2+} influx and intracellular Ca^{2+} release to initiate vascular smooth muscle contractions.[9-11]

Activation of the postsynaptic α_1-adrenoceptor may use either extracellular Ca^{2+}, intracellular Ca^{2+}, or both to initiate contraction and the pathway taken can be dependent on the chemical structure of the α_1-agonist employed to produce the contraction. We have shown previously that there are differences in the responses to α_1-agonist-mediated vasoconstriction produced by two different chemical classes of α_1-agonists.[11] These results suggest that agonists such as methoxamine and SK&F 1-89748 (*l*-1,2,3,4-tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine)[12] primarily use extracellular Ca^{2+} to produce contractions of smooth muscle. α_1-Agonists of a different general structural type, such as phenylephrine or norepinephrine, which have protonic containing substituents on the meta position of the aromatic ring, are able to induce contraction by both translation of extracelular Ca^{2+} and by internal release of Ca^{2+} stores.[13] The compound described in this report, *N*-[2-hydroxy-5-[2-(methylamino)ethyl]phenyl]methanesulfonamide (SK&F 102652) is a selective α_1-adrenoceptor agonist which has

Scheme I



(1) Timmermans, P. B. M. W. M.; van Zwieten, P. A. *J. Med. Chem.* **1982**, *25*, 1389.
(2) McGrath, J. C. *Biochem. Pharmacol.* **1982**, *31*, 467.
(3) Fowler, P. J.; Grous, M.; Price, W.; Matthews, W. D. *J. Pharm. Exp. Ther.*, in press.
(4) Van Meel, J. C. H.; deJonge, A.; Kalkman, H. O.; Wilffert, B.; Timmermans, P. B. M. W. M.; van Zwieten, P. A. *Eur J. Pharmacol.* **1981**, *69*, 205.
(5) Van Meel, J. C. A.; Timmermans, P. B. M. W. M.; van Zwieten, P. A. *J. Cardiovasc. Pharmacol.* **1982**, *5*, 580.
(6) Matthews, W. D.; Jim, K. F.; Hieble, J. P.; DeMarinis, R. M. *Fed. Proc., Fed. Am. Soc. Expl. Biol.* **1984**, *43*, 2923.
(7) Langer, S. Z.; Shepperson, N. B. *Br. J. Pharmacol.* **1980**, *74*, 942.
(8) Llenas, J.; Massingham, R. *J. Pharmacol.* **1983**, *87*, 53.
(9) Cauvin, C.; Loutzenhiser, R.; Hwang, O.; van Breeman, C. *Eur. J. Pharmacol.* **1982**, *84*, 233.
(10) Langer, S. Z.; Shepperson, N. B. *Trends Pharmacol. Sci.* **1982**, *3*, 440.
(11) Jim, K. F.; Matthews, W. D. *Pharmacologist* **1983**, *25*(3), 136.

0022-2623/85/1828-0245$01.50/0

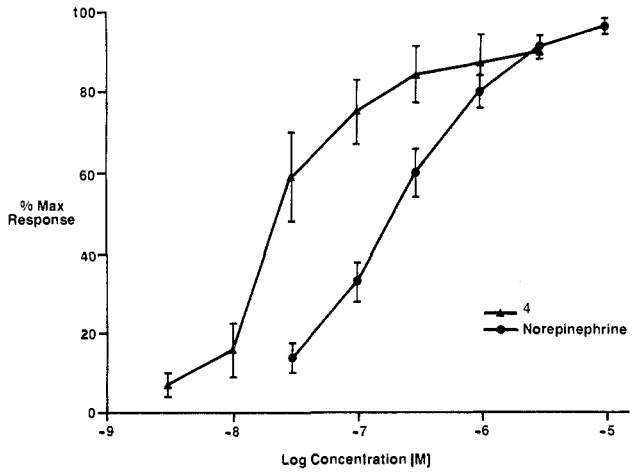


Figure 1. Effects of 4 and norepinephrine on the constrictor response of the isolated perfused rabbit ear artery segment. Each point represents the mean of four experiments ± SEM.

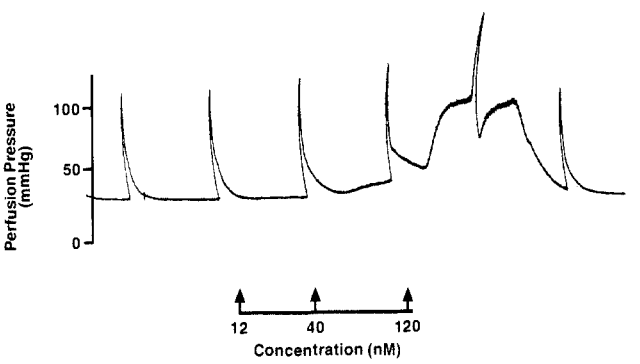


Figure 2. Effect of increasing concentrations of 4 on the constrictor response of the isolated perfused rabbit ear artery to field stimulation.

the ability to initiate vascular smooth muscle contraction almost entirely by release of Ca^{2+} from internal stores. This agent is the best of a series of compounds which have been evaluated in our laboratory for their ability to release intracellular calcium. It is superior in this respect to either the nonselective endogenous ligand norepinephrine or the classically used α_1-agonist phenylephrine and it should be of utility as a tool to help elucidate the role of Ca^{2+} in α-receptor-mediated constriction of vascular smooth muscle.

Chemistry. The compound of interest was synthesized in seven steps in an overall yield of 12% from previously reported *p*-hydroxy-*m*-nitrophenylacetic acid[14] as shown in Scheme I. It was characterized as a crystalline hydrobromide salt.[15]

Results and Discussion

The α_1-adrenergic potency of 4 as well as that of the endogenous transmitter norepinephrine in the isolated rabbit ear artery segment is shown in Figure 1. In these experiments 4 has an EC_{50} of 25 nM, making it about 8 times more potent than norepinephrine. In this tissue

Table I. Effects of Zero External Ca^{2+} on the Contractions Induced by α_1-Agonists in the Canine Saphenous Vein[a]

α-agonists	agonist contractions[b] EC_{25}	EC_{50}	EC_{100}
norepinephrine	6.7 ± 1.8	9.3 ± 0.9	14.5 ± 0.4
phenylephrine	4.4 ± 1.3	7.3 ± 0.7	14.3 ± 0.7
4	6.0 ± 0.8[c]	20.2 ± 1.8[d]	37.9 ± 1.4[e]

[a] Experiments done in the presence of 2 mM EGTA and are the mean of six experiments ± SEM. [b] Values are expressed as percent of control response in 2.5 mM Ca^{2+} physiological saline. [c] Absolute concentration 1.5 ± 0.7 × 10^{-7} M. [d] Absolute concentration 5.0 ± 1.5 × 10^{-7} M. [e] Absolute concentration 5.0 × 10^{-5} M.

Table II. Effects of 1 μM External Ca^{2+} on the Contraction Induced by α_1-Agonists in the Canine Saphenous Vein[a]

α-agonists	agonist contractions[b] EC_{25}	EC_{50}	EC_{100}
norepinephrine	6.3 ± 1.6	9 ± 1.0	45.3 ± 7.4
phenylephrine	6.0 ± 2.1	9.6 ± 2.4	35.7 ± 3.4
4	8.1 ± 1.2[c]	37.6 ± 4.8[d]	78.3 ± 5.3[e]

[a] Values are the mean of six experiments ± SEM. [b] Values are expressed as percent of control response in 2.5 mM Ca^{2+}. [c] Absolute concentration = 1.5 ± 0.3 × 10^{-7}. [d] Absolute concentration = 5.0 ± 1.5 × 10^{-7} M. [e] Absolute concentration = 5.0 × 10^{-5} M.

compound 4 appears to be a full agonist which produces a response equal to the maximum response elicited by norepinephrine. The constrictor response to 4 is blocked competitively by phentolamine with a dissociation constant of <20 nM, which would be expected for α-mediated events.

The data from Figure 2 illustrate that compound 4 is selective for α_1 vis a' vis α_2 receptors. Under conditions of electrical stimulation, adrenergic nerves are activated, causing release of norepinephrine, which produces the contractile response. Activation of presynaptic α_2-adrenoceptors on noradrenergic nerve terminals initiates a negative feedback loop, which inhibits the further release of norepinephrine evoked by electrical stimulation. This results in an inhibition of neurotransmission, which is manifested by a decrease in the constrictor response to nerve stimulation. As the data in Figure 2 show, there is no appreciable diminution of neurotransmission produced by 4 at concentrations over 30 times that required for α_1-adrenoceptor-mediated vasoconstriction. Quantification of this selectivity using the isolated perfused guinea pig atrium preparation[16] that this compound has no appreciable α_2-agonist activity up to 1200 nM and thus shows a selectivity ratio α_1/α_2 of ≥48.

This agent induces its physiological response through a pathway that is substantially different from that used by some other agonists. Previous studies have suggested that α_1-agonists can be subdivided into two general classes on the basis of their ability to translocate Ca^{2+} or release it from internal stores.[11] Representative of the class of agents that translocate Ca^{2+} are methoxamine and SK&F 1-89748-A [*l*-1,2,3,4-tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine].[12] These are agonists whose aromatic rings contain no hydroxyl or hydroxyl equivalents. On the other hand, compounds such as norepinephrine, phenylephrine, and 4 all contain protonic (hydroxyl or hydroxyl substitute) substituents on the 3-

(12) DeMarinis, R. M.; Hieble, J. P. *J. Med. Chem.* **1983**, *26*, 1215.
(13) Jim, K. F.; DeMarinis, R. M.; Matthews, W. D. *Eur. J. Pharmacol.*, in press.
(14) *Chem. Abstr.* **1964**, *61*, 13359b.
(15) This compound has been disclosed as the corresponding hydrochloride in U.S. Patent 3 574 741 issued to W. A. Gould and A. A. Larsen. No experimental details are reported. The compound is claimed to be a pressor amine which is in agreement with the α_1-agonist activity described by us.
(16) Hieble, J. P.; Pendleton, R. G. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1979**, *309*, 217.
(17) Sarda, K.; van Breeman, C. *Pflugers Arch.* **1983**, *397*, 166.
(18) DeMarinis, R. M.; Shah, D. H.; Hall, R. F.; Hieble, J. P.; Pendleton, R. G. *J. Med. Chem.* **1982**, *25*, 136.

position of the aromatic ring and have varying abilities to release intracellular Ca^{2+}. Among the latter class of reagents which can release intracellular Ca^{2+} stores, compound 4 is the best of a series of agents that have been evaluated. It is superior to the nonselective α_1-agonist norepinephrine as well as to the selective α_1-agonist phenylephrine.

The data in Tables I and II show that even among the class of phenylethylamines which are able to use internal as well as external calcium, alterations of the external Ca^{2+} concentration had dramatic effects on the contraction induced by α_1-agonists. In the presence of zero external Ca^{2+} norepinephrine and phenylephrine are able to produce significant though greatly reduced contractions of smooth muscle relative to that produced in the presence of normal Ca^{2+}. At an EC_{50} concentration for normal Ca^{2+}-containing conditions these agents produce only 7–9% of this maximum while 4 elicits over twice this absolute response, producing 20% of maximum. At very high concentration where a 100% response is possible, the differences are also significant. Under these conditions, compound 4 generates almost 3 times the response of equieffective concentrations of norepinephrine or phenylephrine (38% vs. 14%).

In conditions of reduced Ca^{2+} concentration (1 μM, Table II) rather than zero Ca^{2+}, interesting effects are also observed. At low concentrations (EC_{50}) compound 4 is 4 times as effective as phenylephrine (38% vs. 9%) and at EC_{100} concentrations it produces 78% of the potential maximal response under normal calcium concentrations. This low Ca^{2+} concentration (1 μM) may serve as a source of trigger Ca^{2+} necessary for initiating further internal release in a process in which the ion released from a loosely bound membrane pool in turn triggers the further release of Ca^{2+} from intracellular stores.[17]

The data from these studies clearly demonstrate that 4 is a selective α_1-agonist which is able to use internal calcium to effect vascular smooth muscle contraction. It is one of the most effective agents we have observed in carrying out this process and is superior to both phenylephrine and norepinephrine. It should be a useful tool for helping to clarify the role of calcium in α-adrenergically mediated events.

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover Uni-melt apparatus and are uncorrected. Elemental analyses were performed by the Analytical, Physical and Structural Chemistry Department of Smith Kline & French Laboratories. Where analyses are reported by symbols of elements, results were within 0.4% of calculated values. Satisfactory IR and NMR spectra were obtained for all new compounds.

Determination of α_1- and α_2-Agonist Activity. Quantitative in vitro determination of α_1-adrenergic potency in the rabbit ear artery was carried out as described previously.[18] Quantitative in vitro determination of α_2-adrenergic potency in the guinea pig atrium was also carried out as described previously.[16]

General Protocol for Measurement of Ca^{2+}-Dependent Contraction. Rings of canine saphenous vein (CSV) were equilibrated in physiological saline solution (PSS) at 37 °C for 1 h, with a change of solution every 15 min. After this equilibration period, contractions to cumulative concentrations of α-agonists were recorded. Drugs were administered in increasing concentrations, and the concentration was increased only when the previous concentration had produced a maximum response. For each agonist, the results were expressed as a percentage of its own maximum contraction. The concentrations that produce 25% (EC_{25}), 50% (EC_{50}), and 100% (EC_{100}) of the maximum contraction to each α-agonist were then calculated as the geometric mean values from the concentration–response curves. Each tissue was exposed to only one agonist.

External Ca^{2+}-Dependence Studies. Rings of CSV were equilibrated for 1 h in PSS at 37 °C, and contractions to the EC_{50} concentration of an α-agonist were measured. The tissues were washed and reequilibrated in PSS for 1 h, and single maximum contraction to an α-agonist was determined as the control EC_{100} response under normal Ca^{2+} concentration. The tissues were washed until the muscles relaxed to the base-line tension, and reequilibrated in PSS for an additional 30 min, with a change of solution every 10 min. Preliminary studies showed that there was no change in agonist sensitivity after this washing and reequilibration procedure. The tissues were washed twice with PSS containing 1 μM Ca^{2+} and equilibrated in this solution for 5 min. Single maximum contraction to the α-agonist was determined in this reduced Ca^{2+} concentration. The results were expressed as a percentage of the contraction in buffer containing normal (2.5 mM) Ca^{2+}. A similar procedure was used to measure the contractions in Ca^{2+}-free PSS containing 2 mM EGTA (zero Ca^{2+}).

In separate experiments, the external Ca^{2+} dependence of contractions to lower concentrations (EC_{25} and EC_{50}) of the α-agonist was determined. Two initial contractions to the agonist (EC_{25} or EC_{50}) were determined in normal Ca^{2+} condition and the second contraction was used as the control response. The procedure above was then used to determine the contractions in 1 μM Ca^{2+} and zero Ca^{2+}. Each tissue was exposed to only one agonist.

4-Hydroxy-*N*-methyl-3-nitrobenzeneacetamide (2). A mixture of 40 g (0.2 mol) of 3-nitro-4-hydroxyphenylacetic acid[14] in 50 mL of thionyl chloride was refluxed for 45 min. It was cooled and poured into 500 mL of hexane. The resulting precipitate was collected by filtration, washed with hexane, and air-dried to give 40.6 g (100%) of yellow crystals. A solution of 9.7 g (0.048 mol) of this acid chloride in 100 mL of CH_2Cl_2 was cooled in an ice bath and stirred while excess methylamine was distilled in dropwise. The mixture was stirred at room temperature overnight. The precipitated solid was collected by filtration and dissolved in water. It was acidified to pH 2.0 with 3 N HCl and the amide crystallized as yellow needles, mp 127–128.5 °C, 7.6 g (75%).[19] Anal. ($C_9H_9NO_5$) C, H, N.

4-Methoxy-*N*-methyl-3-[(methylsulfonyl)amino]benzeneacetamide (3). To a solution of 7.5 g (0.036 mol) of phenol 2 in 75 mL of DMF containing 20 g of anhydrous potassium carbonate was added 13.5 g (0.107 mol) of dimethyl sulfate. The mixture was heated at 60–70 °C for 45 min, treated with an additional 6.65 g of methyl sulfate, and heated for another 30 min. The mixture was cooled, poured into 300 mL of H_2O, and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried, and evaporated to give a solid, which after recrystallization from EtOH–H_2O gave 5.4 g (67%) of yellow plates, mp 113–114 °C. A solution of 5.3 g of this solid was hydrogenated at 50 psi in 50 mL of EtOH over 100 mg of PtO_2 for 6 h. The catalyst was removed by filtration and the solvent evaporated to give 4.6 g (100%) of off-white crystals. Without further purification, they were dissolved in 40 mL of pyridine and treated dropwise with 2.9 g of mesyl chloride in 10 mL of pyridine. The reaction mixture was warmed to 65 °C for 0.5 h and then stirred at room temperature overnight. The pyridine was evaporated and the residue taken up in 40 mL of H_2O, adjusted to pH 6.7, and cooled in an ice bath. The resulting precipitate was removed by filtration and dried to give 2.88 g of an off-white solid. Recrystallization from MeOH gave 2.39 g (52%) of white crystals, mp 156.5–157 °C. Anal. ($C_{11}H_{16}N_2O_4S$) C, H, N.

***N*-[2-Hydroxy-5-[2-(methylamino)ethyl]phenyl]methanesulfonamide (4).** A solution of 2.3 g (9.6 mmol) of 3 in 100 mL of dry THF was stirred and cooled in ice as a 1 M solution of borane in THF (29 mL) was added dropwise. After the addition was complete, the mixture was warmed to 65 °C for 6 h. It was cooled and treated with 50 mL of MeOH followed by 1 mL of 6 N HCl. The mixture was evaporated to a white residue which was dissolved in a minimum amount of hot MeOH, filtered, and treated with EtOAC until cloudy and allowed to crystallize. The solid was removed by filtration and dried to give 1.91 g (68%) of white crystals, mp 156–157 °C. A suspension of 1.68 g (5.7 mmol) of these crystals in 150 mL of CH_2Cl_2 in a dry ice–2-propanol bath was treated with 20.8 mL of 1 M BBr_3 in

(19) Satisfactory IR and NMR spectra as well as C, H, N analyses were obtained for all compounds.

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.

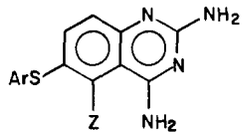
Folate Antagonists. 21. Synthesis and Antimalarial Properties of 2,4-Diamino-6-(benzylamino)pyrido[3,2-*d*]pyrimidines

Norman L. Colbry, Edward F. Elslager, and Leslie M. Werbel*

Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105. *Received March 26, 1984*

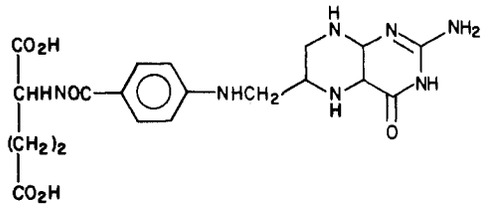
The synthesis and antimalarial activity of a series of 2,4,6-triaminopyrido[3,2-*d*]pyrimidines (4) is described. Several 6-substituted benzylmethylamino analogues were more active against trophozoite induced *Plasmodium berghei* in mice than the corresponding quinazoline analogues. These agents, however, 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

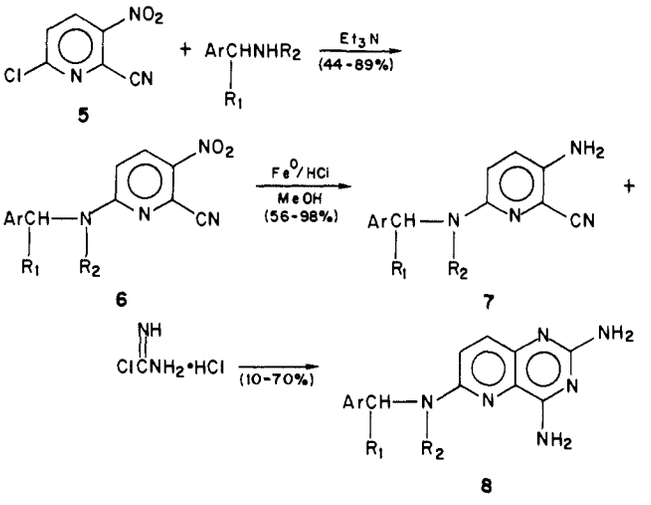
antimetabolites whose architecture, physical properties, and chemical reactivity should more closely resemble the tetrahydrofolate coenzymes 2[4] which are ultimately involved in the biochemistry of the malaria parasite.

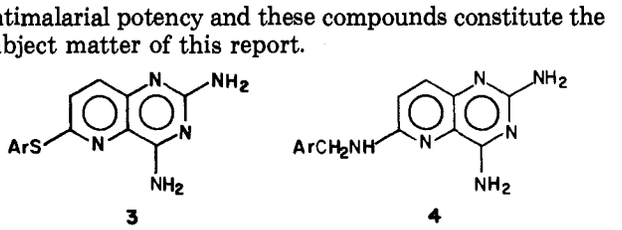


2
(tetrahydrofolic acid)

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

Scheme I





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