

humidity, and 5% CO<sub>2</sub>. Exponentially growing cells ( $4 \times 10^5$  cells/mL) were incubated with test compounds at concentrations of 1, 10, or 100  $\mu$ M. Cell counts were taken at 24, 48, and 72 h. Cell viability was measured by the trypan blue exclusion technique.<sup>16</sup> Stability of all suspensions was monitored throughout the test period by thin-layer chromatography.

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**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 $\alpha_1$ -Adrenoceptors

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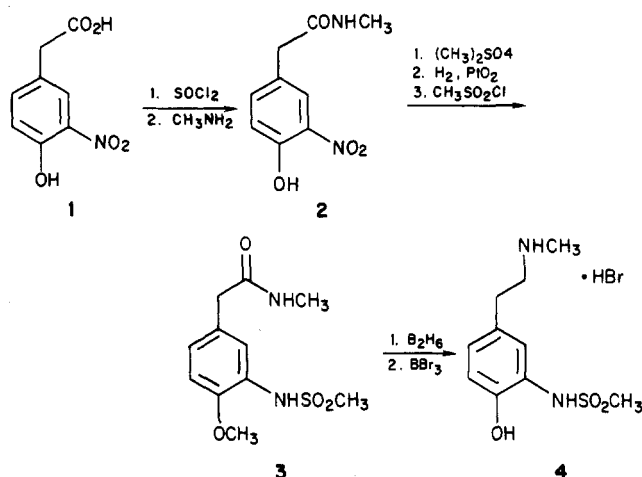
Department of Medicinal Chemistry and Pharmacology, Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101. Received May 9, 1984

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<sub>50</sub> of 25 nM at  $\alpha_1$ -adrenoceptors as determined in the isolated perfused rabbit ear artery. On the presynaptic  $\alpha_2$ -adrenoceptors of the guinea pig atrium it was considerably weaker, demonstrating an EC<sub>50</sub> for inhibition of neurotransmission of 1200 nM and thus an overall  $\alpha_1/\alpha_2$  selectivity ratio of  $\geq 48$ . In the vascular smooth muscle of the canine saphenous vein an EC<sub>100</sub> concentration of this agonist in the presence of zero external Ca<sup>2+</sup> induced  $37.9 \pm 1.4\%$  of the maximal contractile response due to this agent while the endogenous ligand norepinephrine evoked only  $14.5 \pm 0.4\%$  of the maximum. In the presence of low (1  $\mu$ M) external calcium, this agent produced  $78.3 \pm 5.3\%$  of maximum while norepinephrine gave  $45.3 \pm 7.4\%$ . This agent produces  $\alpha_1$ -adrenoceptor-mediated contraction primarily by release of intracellular Ca<sup>2+</sup> and should provide a useful tool for characterizing  $\alpha_1$ -receptor subtypes.

In the last several years, it has been amply demonstrated that two distinct types of postsynaptic  $\alpha$ -adrenoceptors ( $\alpha_1$ ,  $\alpha_2$ ) are present on vascular smooth muscle and that activation of either subtype causes vasoconstriction.<sup>1-3</sup> Evidence has been produced from both in vitro and in vivo experiments to indicate that there is a pharmacological difference in the Ca<sup>2+</sup> utilization process of smooth muscle after stimulation of  $\alpha_1$ - or  $\alpha_2$ -adrenoceptors.<sup>4-6</sup> Studies from a number of laboratories have shown that activation of postsynaptic  $\alpha_2$ -adrenoceptors causes the influx of extracellular Ca<sup>2+</sup> across the cell membrane and that it is this translocation of Ca<sup>2+</sup> that mediates the contractile process.<sup>6-8</sup> On the other hand, activation of postsynaptic  $\alpha_1$ -adrenoceptors can induce both extracellular Ca<sup>2+</sup> influx and intracellular Ca<sup>2+</sup> release to initiate vascular smooth muscle contractions.<sup>9-11</sup>

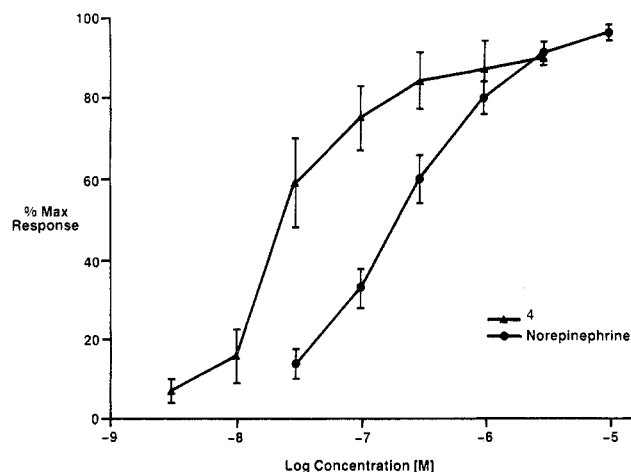
Activation of the postsynaptic  $\alpha_1$ -adrenoceptor may use either extracellular Ca<sup>2+</sup>, intracellular Ca<sup>2+</sup>, or both to

Scheme I

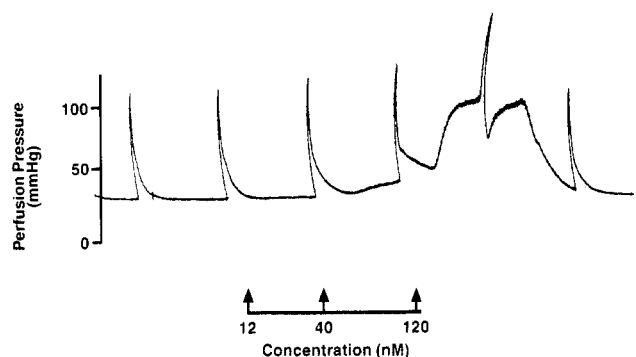


initiate contraction and the pathway taken can be dependent on the chemical structure of the  $\alpha_1$ -agonist employed to produce the contraction. We have shown previously that there are differences in the responses to  $\alpha_1$ -agonist-mediated vasoconstriction produced by two different chemical classes of  $\alpha_1$ -agonists.<sup>11</sup> These results suggest that agonists such as methoxamine and SK&F 1-89748 (1-1,2,3,4-tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine)<sup>12</sup> primarily use extracellular Ca<sup>2+</sup> to produce contractions of smooth muscle.  $\alpha_1$ -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 extracellular Ca<sup>2+</sup> and by internal release of Ca<sup>2+</sup> stores.<sup>13</sup> The compound described in this report, N-[2-hydroxy-5-[2-(methylamino)ethyl]phenyl]methanesulfonamide (SK&F 102652) is a selective  $\alpha_1$ -adrenoceptor agonist which has

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**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  $\pm$  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  $\text{Ca}^{2+}$  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  $\alpha_1$ -agonist phenylephrine and it should be of utility as a tool to help elucidate the role of  $\text{Ca}^{2+}$  in  $\alpha$ -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<sup>14</sup> as shown in Scheme I. It was characterized as a crystalline hydrobromide salt.<sup>15</sup>

## Results and Discussion

The  $\alpha_1$ -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  $\text{EC}_{50}$  of 25 nM, making it about 8 times more potent than norepinephrine. In this tissue

**Table I.** Effects of Zero External  $\text{Ca}^{2+}$  on the Contractions Induced by  $\alpha_1$ -Agonists in the Canine Saphenous Vein<sup>a</sup>

$\alpha$ -agonists	agonist contractions <sup>b</sup>		
	$\text{EC}_{25}$	$\text{EC}_{50}$	$\text{EC}_{100}$
norepinephrine	$6.7 \pm 1.8$	$9.3 \pm 0.9$	$14.5 \pm 0.4$
phenylephrine	$4.4 \pm 1.3$	$7.3 \pm 0.7$	$14.3 \pm 0.7$
4	$6.0 \pm 0.8^c$	$20.2 \pm 1.8^d$	$37.9 \pm 1.4^e$

<sup>a</sup> Experiments done in the presence of 2 mM EGTA and are the mean of six experiments  $\pm$  SEM. <sup>b</sup> Values are expressed as percent of control response in 2.5 mM  $\text{Ca}^{2+}$  physiological saline. <sup>c</sup> Absolute concentration  $1.5 \pm 0.7 \times 10^{-7}$  M. <sup>d</sup> Absolute concentration  $5.0 \pm 1.5 \times 10^{-7}$  M. <sup>e</sup> Absolute concentration  $5.0 \times 10^{-5}$  M.

**Table II.** Effects of 1  $\mu\text{M}$  External  $\text{Ca}^{2+}$  on the Contraction Induced by  $\alpha_1$ -Agonists in the Canine Saphenous Vein<sup>a</sup>

$\alpha$ -agonists	agonist contractions <sup>b</sup>		
	$\text{EC}_{25}$	$\text{EC}_{50}$	$\text{EC}_{100}$
norepinephrine	$6.3 \pm 1.6$	$9 \pm 1.0$	$45.3 \pm 7.4$
phenylephrine	$6.0 \pm 2.1$	$9.6 \pm 2.4$	$35.7 \pm 3.4$
4	$8.1 \pm 1.2^c$	$37.6 \pm 4.8^d$	$78.3 \pm 5.3^e$

<sup>a</sup> Values are the mean of six experiments  $\pm$  SEM. <sup>b</sup> Values are expressed as percent of control response in 2.5 mM  $\text{Ca}^{2+}$ . <sup>c</sup> Absolute concentration  $= 1.5 \pm 0.3 \times 10^{-7}$  M. <sup>d</sup> Absolute concentration  $= 5.0 \pm 1.5 \times 10^{-7}$  M. <sup>e</sup> Absolute concentration  $= 5.0 \times 10^{-5}$  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  $\alpha$ -mediated events.

The data from Figure 2 illustrate that compound 4 is selective for  $\alpha_1$  vis  $\alpha'$  vis  $\alpha_2$  receptors. Under conditions of electrical stimulation, adrenergic nerves are activated, causing release of norepinephrine, which produces the contractile response. Activation of presynaptic  $\alpha_2$ -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  $\alpha_1$ -adrenoceptor-mediated vasoconstriction. Quantification of this selectivity using the isolated perfused guinea pig atrium preparation<sup>16</sup> that this compound has no appreciable  $\alpha_2$ -agonist activity up to 1200 nM and thus shows a selectivity ratio  $\alpha_1/\alpha_2$  of  $\geq 48$ .

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  $\alpha_1$ -agonists can be subdivided into two general classes on the basis of their ability to translocate  $\text{Ca}^{2+}$  or release it from internal stores.<sup>11</sup> Representative of the class of agents that translocate  $\text{Ca}^{2+}$  are methoxamine and SK&F 1-89748-A [*l*-1,2,3,4-tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine].<sup>12</sup> 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-

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(15) This compound has been disclosed as the corresponding hydrochloride in U.S. Patent 3574741 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  $\alpha_1$ -agonist activity described by us.

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position of the aromatic ring and have varying abilities to release intracellular  $\text{Ca}^{2+}$ . Among the latter class of reagents which can release intracellular  $\text{Ca}^{2+}$  stores, compound 4 is the best of a series of agents that have been evaluated. It is superior to the nonselective  $\alpha_1$ -agonist norepinephrine as well as to the selective  $\alpha_1$ -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  $\text{Ca}^{2+}$  concentration had dramatic effects on the contraction induced by  $\alpha_1$ -agonists. In the presence of zero external  $\text{Ca}^{2+}$  norepinephrine and phenylephrine are able to produce significant though greatly reduced contractions of smooth muscle relative to that produced in the presence of normal  $\text{Ca}^{2+}$ . At an  $\text{EC}_{50}$  concentration for normal  $\text{Ca}^{2+}$ -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  $\text{Ca}^{2+}$  concentration (1  $\mu\text{M}$ , Table II) rather than zero  $\text{Ca}^{2+}$ , interesting effects are also observed. At low concentrations ( $\text{EC}_{50}$ ) compound 4 is 4 times as effective as phenylephrine (38% vs. 9%) and at  $\text{EC}_{100}$  concentrations it produces 78% of the potential maximal response under normal calcium concentrations. This low  $\text{Ca}^{2+}$  concentration (1  $\mu\text{M}$ ) may serve as a source of trigger  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  from intracellular stores.<sup>17</sup>

The data from these studies clearly demonstrate that 4 is a selective  $\alpha_1$ -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  $\alpha$ -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  $\alpha_1$ - and  $\alpha_2$ -Agonist Activity.** Quantitative *in vitro* determination of  $\alpha_1$ -adrenergic potency in the rabbit ear artery was carried out as described previously.<sup>18</sup> Quantitative *in vitro* determination of  $\alpha_2$ -adrenergic potency in the guinea pig atrium was also carried out as described previously.<sup>16</sup>

**General Protocol for Measurement of  $\text{Ca}^{2+}$ -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  $\alpha$ -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% ( $\text{EC}_{25}$ ), 50% ( $\text{EC}_{50}$ ), and 100% ( $\text{EC}_{100}$ ) of the maximum contraction to each  $\alpha$ -agonist were then calculated as the geometric mean values from the concentration–response curves. Each tissue was exposed to only one agonist.

**External  $\text{Ca}^{2+}$ -Dependence Studies.** Rings of CSV were equilibrated for 1 h in PSS at 37 °C, and contractions to the  $\text{EC}_{50}$

concentration of an  $\alpha$ -agonist were measured. The tissues were washed and reequilibrated in PSS for 1 h, and single maximum contraction to an  $\alpha$ -agonist was determined as the control  $\text{EC}_{100}$  response under normal  $\text{Ca}^{2+}$  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  $\mu\text{M}$   $\text{Ca}^{2+}$  and equilibrated in this solution for 5 min. Single maximum contraction to the  $\alpha$ -agonist was determined in this reduced  $\text{Ca}^{2+}$  concentration. The results were expressed as a percentage of the contraction in buffer containing normal (2.5 mM)  $\text{Ca}^{2+}$ . A similar procedure was used to measure the contractions in  $\text{Ca}^{2+}$ -free PSS containing 2 mM EGTA (zero  $\text{Ca}^{2+}$ ).

In separate experiments, the external  $\text{Ca}^{2+}$  dependence of contractions to lower concentrations ( $\text{EC}_{25}$  and  $\text{EC}_{50}$ ) of the  $\alpha$ -agonist was determined. Two initial contractions to the agonist ( $\text{EC}_{25}$  or  $\text{EC}_{50}$ ) were determined in normal  $\text{Ca}^{2+}$  condition and the second contraction was used as the control response. The procedure above was then used to determine the contractions in 1  $\mu\text{M}$   $\text{Ca}^{2+}$  and zero  $\text{Ca}^{2+}$ . 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<sup>14</sup> 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  $\text{CH}_2\text{Cl}_2$  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%).<sup>19</sup> Anal. ( $\text{C}_9\text{H}_9\text{NO}_5$ ) C, H, N.

**4-Methoxy-*N*-methyl-3-[(methylsulfonyl)amino]-benzeneacetamide (3).** To a solution of 7.5 g (0.036 mol) of phenol 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  $\text{H}_2\text{O}$ , and extracted with  $\text{CH}_2\text{Cl}_2$ . The extracts were washed with  $\text{H}_2\text{O}$ , dried, and evaporated to give a solid, which after recrystallization from  $\text{EtOH-H}_2\text{O}$  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  $\text{EtOH}$  over 100 mg of  $\text{PtO}_2$  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  $\text{H}_2\text{O}$ , 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  $\text{MeOH}$  gave 2.39 g (52%) of white crystals, mp 156.5–157 °C. Anal. ( $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$ ) 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  $\text{MeOH}$  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  $\text{MeOH}$ , filtered, and treated with  $\text{EtOAc}$  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  $\text{CH}_2\text{Cl}_2$  in a dry ice–2-propanol bath was treated with 20.8 mL of 1 M  $\text{BBr}_3$  in

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

$\text{CH}_2\text{Cl}_2$ . 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. ( $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ ) 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.

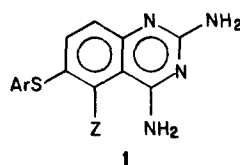
## Folate Antagonists. 21. Synthesis and Antimalarial Properties of 2,4-Diamino-6-(benzylamino)pyrido[3,2-*d*]pyrimidines

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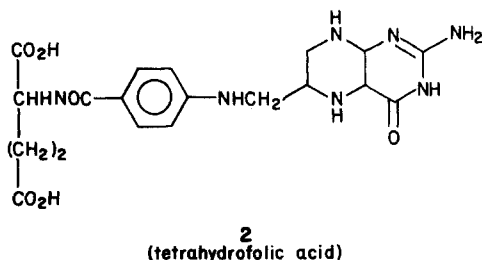
Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105. Received March 26, 1984

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**<sup>3</sup> 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

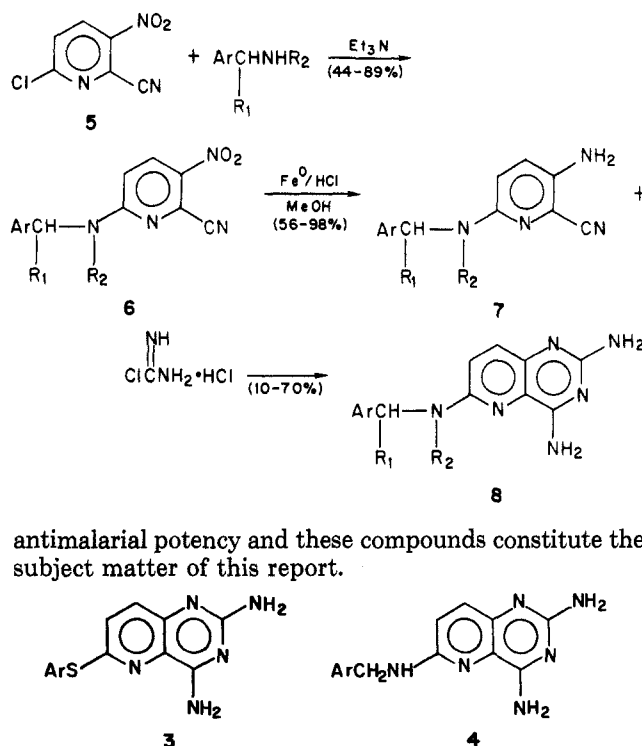


antimetabolites whose architecture, physical properties, and chemical reactivity should more closely resemble the tetrahydrofolate coenzymes **2**<sup>4</sup> which are ultimately involved in the biochemistry of the malaria parasite.



Initial efforts leading to the 2,4-diamino-6-[(arylthio, sulfinyl, and sulfonyl)]pyrido[3,2-*d*]pyrimidines (**3**)<sup>1</sup> 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.

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 chloroformamide 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.
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- (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.