# Folate Antagonists. 22. Antimalarial and Antibacterial Effects of 2,4-Diamino-6-quinazolinesulfonamides[1,2]

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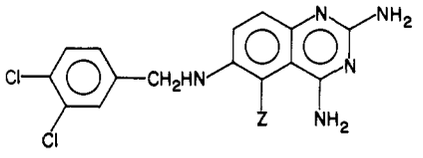
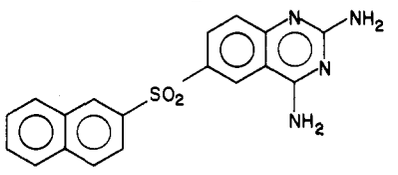
The synthesis and antimalarial activity of a series of 2,4-diamino-6-quinazolinesulfonamides (III) is described. Chlorosulfonation of 2,4-quinazolinediamine affords the 6-sulfonyl chloride, which upon treatment with the appropriate amine produces the desired products. Alternatively the sulfonyl chloride could be introduced by diazotization of the corresponding amine followed by treatment with $SO_2$ in the presence of $CuCl_2$. Although substantial antimalarial activity was demonstrated for several members of this class, studies were discontinued in light of the potency of related series.

The potent antimalarial activity of the $N^6$-(phenylmethyl)-2,4,6-quinazolinetriamines I led to the assessment of replacement of the $-CH_2HN-$ linkage with various biospacers such as $-NH-$, $-CH_2CH_2-$, $-CH{=}CH-$, $-CONH$, $-SO_2NH-$, $-N{=}N-$. This was invariably accompanied, however, by marked reduction or elimination of antimalarial activity,[3] pointing out the importance of this site for binding to the probable primary enzyme of importance for the action of these compounds, i.e., dihydrofolate reductase.

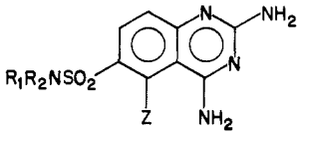


I



II

The even greater activity uncovered with the development of the 6-arylthio analogues represented by II, demonstrating the utility of a S spacer coupled with the possibility of introducing a dual inhibitory mechanism; i.e., inhibition of PABA incorporation along with DHFR inhibition encouraged the preparation of a series of 2,4-diamino-6-quinazolinesulfonamides III. The synthesis and biological activity of this series are the subjects of this paper.

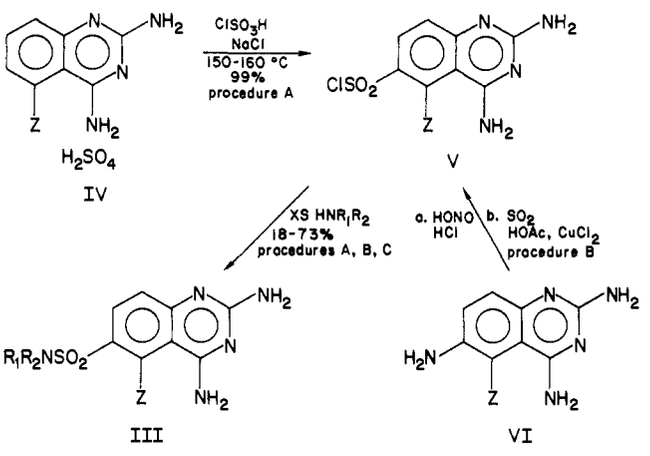


III

$R_1$=H, alkyl, aryl, arylmethyl
$R_2$=H, alkyl
Z=H, Cl, $CH_3$

**Chemistry.** The 2,4-diamino-6-quinazolinesulfonamides are obtained as depicted in Scheme I. Chlorosulfonation of 2,4-quinazolinediamine[4] as the sulfate salt IV affords

**Scheme I**



2,4-diamino-6-quinazolinesulfonyl chloride, sulfate salt[5] (V) (procedure A), which is then allowed to react with an excess of the appropriate amine (procedures A and C), to produce the desired 2,4-diamino-6-quinazolinesulfonamides III (Table I, **1**, **2**, **5**, **7–26**). In three cases, in which the quinazoline ring is substituted at the 5-position with a chloro or methyl substituent (III, Table I, **3**, **4**, **6**), the intermediate sulfonyl chlorides V (Z = Cl, $CH_3$) are prepared by the diazotization of the 5-chloro- or 5-methyl-2,4,6-quinazolinetriamine[6] followed by treatment with sulfur dioxide in the presence of cupric chloride.[7]

**Suppressive Antimalarial Screening in Mice.** The 2,4-diamino-6-quinazolinesulfonamides III (**1–26**) were tested against a normal drug-sensitive strain of *Plasmodium berghei* in mice by the parenteral route.[8,9] The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72-h postinfection. The antimalarial activities are summarized in Table II.

Extension of the mean survival time of the treated mice is interpreted as evidence of antimalarial activity.[8] Compounds are arbitrarily considered to be "active" when they produce at least a 100% increase in the mean survival time of treated mice. Animals that survive to 60 days are considered "cured".

The antimalarial structure–activity patterns were quite unlike those observed among the $N^6$-(phenylmethyl)-2,4,6-quinazoliinetriamines. Thus, antimalarial potency

(1) This is paper 58 of a series on antimalarial drugs. For paper 57 and 21, see: Colbry, N. L.; Elslager, E. F.; Werbel, L. M. *J. Med. Chem.*, in press.

(2) This investigation was supported by the U.S. Army Medical Research and Development Command Contracts DA 49-193-MD-2754 and DADA 17-72-C-2077. This is Contribution No. 1698 to the Army Research Program in Antiparasitic Drugs.

(3) Elslager, E. F.; Davoll, J. In "Lectures in Heterocyclic Chemistry"; Castle, R. N., Townsend, L. B., Eds.; Hetero Corporation, Orem, UT, 1974; Vol. 2, pp S97–S133.

(4) Dymek, N.; Sybistowicz, D. *Monatsh. Chem.* **1965**, *96*, 542.

(5) British Patent 1 143 290, February 19, 1969.

(6) Davoll, J.; Johnson, A. M. *J. Chem. Soc. C* **1970**, 997.

(7) Feit, R. W.; Nielsen, D. B. T. *J. Med. Chem.* **1972**, *15*, 83.

(8) The parenteral antimalarial screening in mice was carried out by Dr. 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.

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

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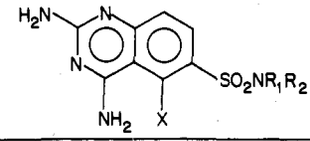
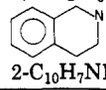
**Table I.** 2,4-Diamino-6-quinazolinesulfonamides



| no. | $NR_1R_2$ | X | mp, °C | yield, % | procedure | recrystn solvent | formula | anal.[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | $NH_2$ | H | 324 dec | 35[g] | A | aq EtOH | $C_8H_9N_5O_2S$ | C, H, N |
| 2 | $N(CH_3)_2$ | H | 275–277 | 47[g] | A | aq EtOH | $C_{10}H_{13}N_5O_2S$ | C, H, N[b] |
| 3 | $N(CH_3)_2$ | $CH_3$ | 274–276 dec | 42[h] | B | aq EtOH | $C_{11}H_{15}N_5O_2S$ | C, H, N |
| 4 | $N(CH_3)_2$ | Cl | 272–274 | 35[h] | B | aq EtOH | $C_{10}H_{12}ClN_5O_2S$ | C, H, N |
| 5 | $N(C_2H_5)_2$ | H | 285–289 | 25[g] | A | aq EtOH | $C_{12}H_{17}N_5O_2S$ | C, H, N |
| 6 | $N(C_2H_5)_2$ | Cl | 218–220 | 18[h] | B | aq EtOH | $C_{12}H_{16}ClN_5O_2S$ | C, H, N, Cl |
| 7 | $N(CH_2CH_2CH_3)_2$ | H | >300 dec | 53[g] | A | aq EtOH | $C_{14}H_{21}N_5O_2S \cdot H_2O$ | C, H, N |
| 8 | $N(CH_2CH_2OH)_2$ | H | 214–215 | 32[b] | A | $H_2O$ | $C_{12}H_{17}N_5O_4S$ | C, H, N |
| 9 | $N(CH_3)CH(CH_3)_2$ | H | 285–287 dec | 34[i] | A | aq EtOH[c] | $C_{12}H_{17}N_5O_2S$ | C, H, N |
| 10 | $N(CH_3)CH_2CH_2N(C_2H_5)_2$ | H | 210–212 | 60[i] | A | $H_2O$[f] | $C_{15}H_{24}N_6O_2S \cdot 0.2H_2O$ | C, H, N, $H_2O$ |
| 11 | $N(CH_2)_5$ | H | 271–274 | 37[i] | A | aq EtOH[c] | $C_{13}H_{17}N_5O_2S$ | C, H, N |
| 12 | $N(CH_2)_4$ | H | 301–303 dec | 30[i] | A | aq EtOH[c] | $C_{12}H_{15}N_5O_2S \cdot 0.2H_2O$ | C, H, N, $H_2O$ |
| 13 | $4\text{-}[N(CH_2)_5]\text{-}N(CH_2)_5$ | H | 274–278 dec | 45[i] | A | aq EtOH[c] | $C_{18}H_{26}N_6O_2S \cdot 0.2H_2O$ | C, H, N, $H_2O$ |
| 14 | $N\text{-}[(CH_2)_2]_2O$ | H | 282–284 | 58[i] | A | DMF + EtOH | $C_{12}H_{15}N_5O_3S$ | C, H, N |
| 15 | $N[(CH_2)_2]_2S$ | H | 268–272 | 64[i] | A | aq EtOH[c] | $C_{12}H_{15}N_5O_2S_2$ | C, H, N |
| 16 | $N[(CH_2)_2]_2NCH_3$ | H | 290–292 | 41[i] | A | aq EtOH[c] | $C_{13}H_{18}N_6O_2S$ | C, H, N |
| 17 | $N[(CH_2)_2]_2NC(=O)OC_2H_5$ | H | 218–219 | 55[i] | A | aq EtOH[c] | $C_{15}H_{20}N_6O_4S$ | C, H, N |
| 18 | $2\text{-}(C_6H_5CH_2)\text{-}N(CH_2)_5$ | H | 267–269 | 32[i] | A | aq EtOH[c] | $C_{20}H_{23}N_5O_2S$ | C, H, N |
| 19 | $4\text{-}Cl\text{-}C_6H_4NH$ | H | 327–328 | 37[i] | C | aq EtOH[c] | $C_{14}H_{12}ClN_5O_2S$ | C, H, N |
| 20 | $3,4\text{-}Cl_2\text{-}C_6H_3NH$ | H | 338–340 | 42[i] | C | aq EtOH[c] | $C_{14}H_{11}Cl_2N_5O_2S$ | C, H, N |
| 21 | $3\text{-}Br\text{-}C_6H_4NH$ | H | 313–316 | 41[i] | C | aq EtOH[c] | $C_{14}H_{12}BrN_5O_2S$ | C, H, N |
| 22 | $3\text{-}Cl\text{-}C_6H_4NCH_3$ | H | 270–272 | 45[i] | C | aq EtOH[c] | $C_{15}H_{14}ClN_5O_2S$ | C, H, N |
| 23 | $C_6H_5NCH_3$ | H | 249–251 | 62[i] | C | aq EtOH[c] | $C_{15}H_{15}N_5O_2S \cdot {}^2/_3H_2O$ | C, H, N, $H_2O$ |
| 24 | $3,4\text{-}Cl_2\text{-}C_6H_3CH_2NCH_3$ | H | 289–291 | 36[i] | C | $NH_4OH$, aq EtOH[e] | $C_{16}H_{15}Cl_2N_5O_2S$ | C, H, N |
| 25 |  | H | 268–270 | 37[i] | C[j] | DMF | $C_{17}H_{17}N_5O_2S$ | C, H, N |
| 26 | $2\text{-}C_{10}H_7NH$ | H | 348–350 | 27[i] | C | aq EtOH,[c] DMF–$H_2O$ | $C_{18}H_{15}N_5O_2S$ | C, H, N[f] |

[a] Analyses within ±0.4% for indicated elements, except as noted. [b] H: calcd, 4.9; found, 5.4. [c] A few drops of concentrated $NH_4OH$ were added to the recrystallization mixture to effect solution. [d] Crystallized from the reaction mixture. [e] Trituration. [f] N: calcd, 19.17; found, 19.52. [g] From the 2,4-quinazolinediamine. [h] From the 2,4,6-quinazolinetriamine. [i] From 2,4-diaminoquinazoline-6-sulfonyl chloride sulfate. [j] Reaction solvent was 50% aqueous EtOH.

was optimal among lower *N*-monoalkyl and *N,N*-dialkyl derivatives (i.e., compounds **2**, **5**, **12**, **14**) and was not enhanced by 5-substitution. The most potent compound appeared to be the morpholino analogue *14*. Moreover, 2,4-diamino-*N*-(3,4-dichlorophenyl)-6-quinazolinesulfonamide (**20**), the bioisostere of I, proved to be less active than the simple alkyl-6-quinazolinesulfonamides. The unsubstituted sulfonamide **1** was devoid of antimalarial activity. In general, the sulfonamides clearly exhibit a lower order of potency than the I type or the 6-arylthio analogues II.

**Antibacterial Studies.** Most of the 2,4-diamino-6-quinazolinesulfonamides (**1**, **3**, **4**, **6**, **10–18**, **20–26**) were also tested in vitro against a spectrum of pathogenic bacteria including *Streptococcus faecalis* (MGH-2), normal (U-C-76), and drug-resistant (S18713) *Staphylococcus aureus*, *Pseudomonas aeruginosa* (28), *Escherichia coli* (Vogel), *Shigella sonnei* (C-10), and *Mycobacterium tuberculosis* $H_{37}Rv$ (Table III). A modification of the gradient-plate procedure of Szybalski[10] and Webb and Washington[11] was employed throughout.

Although none was particularly effective against *P. aeruginosa* (28), *S. sonnei*, or *M. tuberculosis*, a variety of analogues inhibited the growth of *S. faecalis* and several were effective against *S. aureus* (UC-76), *S. aureus* (S18713), and *E. coli*. These results are presented in Table III.

**Conclusion.** Although substantial antimalarial activity was demonstrated for a number of compounds of this structural class, and in fact several were at least equal to cycloguanil or pyrimethamine, the potency of related series led to deferment of further study in this area.

## Experimental Section

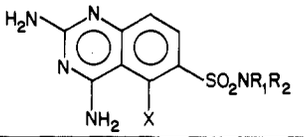
Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Satisfactory infrared spectra were obtained for all compounds.

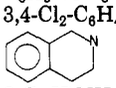
**Procedure A. 2,4-Diamino-*N,N*-dimethyl-6-quinazolinesulfonamide (2, Table I).** To a hot solution of 22.6 g (0.14 mol) of 2,4-quinazolinediamine[4] in 750 mL of $H_2O$ was added 20 mL of concentrated $H_2SO_4$ in 60 mL of $H_2O$. The solution was cooled to afford 27.5 g (75%) of the sulfate salt of 2,4-quinazolinediamine IV, mp 346–348 °C. To a stirring, ice-cooled suspension of 1 g of NaCl in 30 mL of chlorosulfuric acid was added, in portions, 13.85 g (0.05 mol) of 2,4-quinazolinediamine sulfate. The resulting mixture was heated at 150–160 °C for 3 h, cooled, and then poured onto ice. The resulting precipitate was collected and washed with water to afford 19.1 g (99%) of 2,4-diamino-6-quinazolinesulfonyl chloride, sulfate salt, mp >300 °C. A mixture of this material and 180 mL (0.82 mol) of 30% aqueous dimethylamine was heated on the steam bath for 1 h and allowed to cool. The solid was collected, washed with water, dried, and recrystallized from 70% aqueous EtOH to afford 8.4 g (47%) of **2** as white needles.

**Procedure B. 2,4-Diamino-*N*,*N*,5-trimethyl-6-quinazolinesulfonamide (3).** To a thick paste of 2.0 g (0.007 mol) of 5-methyl-2,4,6-quinazolinetriamine[6] in 2.5 mL of concentrated HCl and 1.5 mL of $H_2O$ at 0–5 °C was added, with stirring, a solution of 0.48 g (0.007 mol) of $NaNO_2$ in 0.5 mL of $H_2O$. The sides of the reaction beaker were flushed with 1 mL of $H_2O$ and 1 mL of concentrated HCl. The resulting slurry was allowed to remain at 0 °C for 20 min and then poured into a freshly prepared, cold solution of 4.5 g of $SO_2$ in 7.5 mL of HOAc. To the mixture was added a solution of 0.48 g (0.003 mol) of $CuCl_2 \cdot 2H_2O$ in 0.5 mL of $H_2O$. The reaction mixture was allowed to warm to room temperature (1 h), diluted with a little $H_2O$, and filtered to collect 1.4 g of crude 2,4-diamino-5-methyl-6-

(10) Szybalski, W. *Microb. Genet. Bull.* **1951**, *5*, 16.
(11) Webb, A. H.; Washington, L. *Bacteriol. Proc.* **1966**, *52*, 1188.

**Table II.** Parenteral Suppressive Antimalarial Effects of 2,4-Diamino-6-quinazolinesulfonamides



| no. | $NR_1R_2$ | X | ΔMST; Cor $T^a$ after single sc dose, mg/kg | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 640 | 320 | 160 | 80 | 40 | 20 |
| 1 | $NH_2$ | H | 0.3 | | 0.3 | | 0.1 | |
| 2 | $N(CH_3)_2$ | H | | C5 | 15.9; C2 | 16.1 | 8.7 | 7.3 |
| 3 | $N(CH_3)_2$ | $CH_3$ | T5 | | T5 | | 1.1 | |
| 4 | $N(CH_3)_2$ | Cl | C6(T4)/10 | 23.9; C3 | 17.0; C4/10 | 12.2; C2 | 10.3; C2/10 | 7.5 |
| 5 | $N(C_2H_5)_2$ | H | C5 | C5 | 9.4; C3 | 4.3 | 3.3 | 0.7 |
| 6 | $N(C_2H_5)_2$ | Cl | T5 | 18.9; T3 | 14.9; T2 | 4.3 | 2.3 | |
| 7 | $N(CH_2CH_2CH_3)_2$ | H | 1.3; T4 | | 0.4; T1 | | 0.3 | |
| 8 | $N(CH_2CH_2OH)_2$ | H | 8.1 | 4.1 | 1.3 | 0.5 | 0.3 | 0.3 |
| 9 | $N(CH_3)CH(CH_3)_2$ | H | | 6.9; C2 | 7.3 | 4.0 | 0.7 | 0.5 |
| 10 | $N(CH_3)CH_2CH_2N(C_2H_5)_2$ | H | 0.3 | | 0.3 | | 0.1 | |
| 11 | $N(CH_2)_5$ | H | C5 | 12.9; C3 | 10.2; C2 | 4.7 | 4.4 | 1.1 |
| 12 | $N(CH_2)_4$ | H | C10/10 | C5 | 8.7; C7/10 | 6.9 | 5.0 | 0.5 |
| 13 | $4\text{-}[N(CH_2)_5]\text{-}N(CH_2)_5$ | H | 3.9 | 2.1 | 0.7 | 0.5 | 0.3 | |
| 14 | $N[(CH_2)_2]_2O$ | H | C10/10 | C5 | C10/10 | 14.5 | 4.7 | 1.7 |
| 15 | $N[(CH_2)_2]_2S$ | H | 12.6; C6/10 | 9.6; C2 | 8.3; C2/10 | 3.5 | 2.5 | 1.7 |
| 16 | $N[(CH_2)_2]_2NCH_3$ | H | 11.8 | 8.9 | 4.4 | 1.5 | 1.0 | 0.3 |
| 17 | $N[(CH_2)_2]_2NC(=O)OC_2H_5$ | H | C4/10 | 4.7 | 4.1 | 0.5 | 0.2 | 0.1 |
| 18 | $2\text{-}(C_6H_5CH_2)\text{-}N(CH_2)_5$ | H | 0.5 | | 0.3 | | 0.3 | |
| 19 | $4\text{-}Cl\text{-}C_6H_4NH$ | H | 13.9; C4 | 14.7 | 9.3 | 4.9 | 0.7 | 0.5 |
| 20 | $3,4\text{-}Cl_2\text{-}C_6H_3NH$ | H | C5 | 9.9; C2 | 10.1 | 8.1 | 3.1 | 0.3 |
| 21 | $3\text{-}Br\text{-}C_6H_4NH$ | H | 4.1 | 1.7 | 0.5 | 0.5 | 0.3 | 0.3 |
| 22 | $3\text{-}Cl\text{-}C_6H_4NCH_3$ | H | 11.9 | 6.9 | 4.5 | 0.5 | 0.3 | 0.3 |
| 23 | $C_6H_5NCH_3$ | H | 13.9; C3 | 11.5 | 8.3 | 3.1 | 0.5 | 0.5 |
| 24 | $3,4\text{-}Cl_2\text{-}C_6H_4CH_2NCH_3$ | H | 9.5 | 4.1 | 0.5 | 0.5 | 0.3 | 0.3 |
| 25 |  | H | 6.3 | 3.9 | 0.7 | 0.7 | 0.3 | 0.3 |
| 26 | $2\text{-}C_{10}H_7NH$ | H | 5.3 | 1.5 | 1.1 | 0.5 | 0.3 | 0.3 |
| I[b] | | | T5 | T5 | C5 | C5 | C5 | C5 |
| II | | | C5 | C5 | C5 | C5 | C5 | C5 |
| cycloguanil hydrochloride | | | T5 | C3; T2 | C5 | 21.6; C2 | 13.4; C2 | 7.9 |
| pyrimethamine | | | C1; T2 | C2; T3 | C5 | C3 | C1 | 7.7 |

[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 6.2 days. T signifies the number of toxic deaths occurring on days 2–5 after infection that 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 five-animal group (10 animals when indicated). [b] Structure I where Z = Cl.

**Table III.** In Vitro Antibacterial Effects of 2,4-Diamino-6-quinazolinesulfonamides

| no. | minimum inhib concn,[a] μg/mL | | | | | | |
|---|---|---|---|---|---|---|---|
| | S.f. MGH-2[c] | S.a. UC-76[d] | S.a. S 18713 | P.a. 28[e] | E.c. Vogel[f] | S.s. C-10[g] | M.t. $H37_{Rv}$[h] |
| 1 | I[i] | I | I | I | I | I | N[b] |
| 3 | <0.25 | 2.0 | 2.5 | I | <0.25 | 1.5 | I |
| 4 | <0.25 | 15.0 | I | I | 5.0 | 5.0 | I |
| 6 | <0.25 | 10 | I | I | I | I | I |
| 10 | 20 | I | I | I | I | I | I |
| 11 | <0.25 | <0.25 | <0.25 | I | <0.25 | 0.5 | 10 |
| 12 | <0.25 | <0.25 | 2.0 | I | 10 | I | 10 |
| 13 | I | I | I | I | I | I | I |
| 14 | <0.25 | 2.0 | I | I | I | I | I |
| 15 | <0.25 | <0.25 | <0.25 | I | 2.0 | 2.0 | I |
| 16 | 2.0 | 2.0 | I | I | I | I | I |
| 17 | 2.0 | 2.0 | I | I | I | I | I |
| 18 | <0.25 | 2 | I | I | I | I | I |
| 20 | I | 2.5 | I | I | I | I | I |
| 21 | I | I | I | I | I | I | I |
| 22 | I | I | I | I | I | I | I |
| 23 | I | I | I | I | I | I | I |
| 24 | I | I | I | I | I | I | I |
| 25 | I | I | I | I | I | I | I |
| 26 | 5.0 | I | I | I | I | I | N |

[a] Gradient-plate test. [b] N = not tested. [c] S.f. = *Streptococcus faecalis*. [d] S.a. = *Staphylococcus aureus*. [e] P.a. = *Pseudomonas aeruginosa*. [f] E.c. = *Escherichia coli*. [g] S.c. = *Shigella sonnei*. [h] M.t. = *Mycobacterium tuberculosis*. [i] Minimum inhibitory concentration > 25.

quinazolinesulfonyl chloride of undetermined salt and $H_2O$ content, mp >300 °C. A mixture of this material in 12 mL of 40% aqueous dimethylamine was heated under gentle reflux for 1.5 h, cooled, and filtered to give 0.94 g of crude product **3**. Recrystallization from aqueous EtOH afforded 0.8 g (42%) of **3**, mp 274–276 °C dec.

**Procedure C. 2,4-Diamino-*N*-(4-chlorophenyl)-6-quinazolinesulfonamide (19).** A slurry of 3.6 g (0.01 mol) of

2,4-diamino-6-quinazolinesulfonyl chloride sulfate, 5.1 g (0.04 mol) of 4-chlorobenzenamine, and 50 mL of EtOH was heated under reflux for 1 h, allowed to cool slightly, and poured into $H_2O$. The precipitate was collected and recrystallized from a mixture of EtOH, $H_2O$, and $NH_4OH$ to afford 1.3 g (37%) of **19**, mp 327–328 °C.

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**Registry No.** 1, 21811-06-3; 2, 21811-10-9; 3, 92144-19-9; 4, 92144-20-2; 5, 21882-31-5; 6, 92144-21-3; 7, 21882-32-6; 8, 86670-18-0; 9, 92144-22-4; 10, 92144-23-5; 11, 56044-06-5; 12, 56044-07-6; 13, 92144-24-6; 14, 56044-08-7; 15, 56044-16-7; 16, 56044-10-1; 17, 92144-25-7; 18, 92144-26-8; 19, 92144-27-9; 20, 92144-28-0; 21, 92184-45-7; 22, 92144-29-1; 23, 92144-30-4; 24, 92144-31-5; 25, 56044-17-8; 26, 92144-32-6; IV (Z = H), 81080-73-1; IV (base, Z = H), 1899-48-5; V (Z = H), 92144-33-7; V (Z = Cl), 92144-34-8; V (Z = $CH_3$), 92144-35-9; VI (Z = $CH_3$), 17511-22-7; VI (Z = Cl), 17511-20-5; $NH_3$, 7664-41-7; $HN(CH_3)_2$, 124-40-3; $HN(C_2H_5)_2$, 109-89-7; $HN(CH_2CH_2CH_3)_2$, 142-84-7; $HN(CH_2CH_2OH)_2$, 111-42-2; $NH(CH_3)CH(CH_3)_2$, 4747-21-1; $HN(CH_3)CH_2CH_2N(C_2H_5)_2$, 104-79-0; 4-$ClC_6H_4NH_2$, 106-47-8; 3,4-$Cl_2C_6H_3NH_2$, 95-76-1; 3-$BrC_6H_4NH_2$, 591-19-5; 3-$ClC_6H_4NHCH_3$, 7006-52-2; $C_6H_5NHCH_3$, 100-61-8; 3,4-$Cl_2C_6H_3CH_2NHCH_3$, 5635-67-6; 2-$C_{10}H_7NH_2$, 91-59-8; piperidine, 110-89-4; pyrrolidine, 123-75-1; 1,4′-bipiperidine, 4897-50-1; morpholine, 110-91-8; thromorpholine, 123-90-0; 1-methylpiperazine, 109-01-3; ethyl 1-piperazinecarboxylate, 120-43-4; 2-benzylpiperidine, 32838-55-4; 1,2,3,4-tetrahydroisoquinoline, 91-21-4.

# Tetrahydropyrrolo[1,2-*a*]quinoxalines and Tetrahydropyrrolo[1,2-*a*]pyrido[3,2-*a*]pyrazines: Vascular Smooth Muscle Relaxants and Antihypertensive Agents

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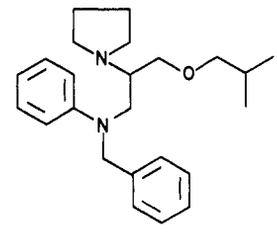
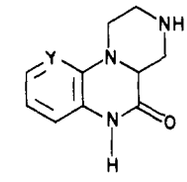
A series of tetrahydropyrrolo[1,2-*a*]quinoxalines and tetrahydropyrrolo[1,2-*a*]pyrido[3,2-*a*]pyrazines were synthesized and tested for their ability to relax $K^+$-depolarized aortic smooth muscle and antihypertensive activity. It was shown that compounds producing the most relaxation of aortic smooth muscle (5-[(2,6-dimethoxyphenyl)methyl]-1,2,3,3a-tetrahydropyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one and 5-[(2,6-dimethoxyphenyl)methyl]-5,6,6a,7,8,9-hexahydropyrrolo[1,2-*a*]pyrazine, **10** and **19**, respectively) demonstrated the least hypotensive activity. Those compounds that were the most effective hypotensive agents (6a,7,8,9-tetrahydro-5-(phenylmethyl)pyrido[3,2-*a*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one and 6a,7,8,9-tetrahydro-5-(4-pyridinylmethyl)pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one, **12** and **13**, respectively) displayed little vascular smooth muscle relaxant activity.

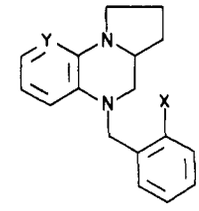
In an effort to develop compounds that inhibit $Ca^{2+}$-dependent force development in vascular smooth muscle with antihypertensive properties, molecular hybrids between the calcium antagonist bepridil[1] (**1**) and the antihypertensive pyrazinoquinoxaline[2] **2a** and tetrahydropyrazino[1,2-*a*]pyrido[3,2-*e*]pyrazines[3,4] **2b** were investigated. The hybrid molecules **3** contain the entire carbon skeleton of **2a** or **2b** but are devoid of the additional piperazino amine functionality. Hybrid compounds **3** also contain most of the carbon skeleton of bepridil but in cyclized form. We hypothesized that the alkyl ether functionality of **1** could be compensated for by the introduction of an ether substituent (X) on the aromatic ring. The hybrid compounds **3a,b** also facilitated an examination of the effects of structural variations on the antihypertensive activities of compounds **2a** and **2b**.



**1**



**2a**, Y = CH
**b**, Y = N



**3a**, Y = CH
**b**, Y = N

**Chemistry.** The key starting intermediates **6** and **7** were prepared by reacting 1-fluoro-2-nitrobenzene or 2-chloro-3-nitropyridine with L-(−)-proline in $Me_2SO$ in the presence of triethylamine at 60 °C to afford the corresponding nitro acids **4** and **5** in 82% and 87% yields, respectively. The nitro acids were reductively cyclized via alkaline sodium dithionite[5] or iron in glacial acetic acid[6] to afford **6** and **7** (Scheme I).

The sodium dithionite reduction was found to be a pH-sensitive reaction; optimum yields (61% for compound **6** and 39% for compound **7**) were obtained at pH 8. Alkylations of **6** and **7** with the appropriately substituted

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