# Synthesis and Antimalarial Properties of 2,4-Diamino-6-[(aryl)thio, sulfinyl, and sulfonyl]pyrido[3,2-*d*]pyrimidines [1,2]



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The synthesis and antimalarial activity of a series of 2,4-diamino-6-[(aryl)thio, sulfinyl and sulfonyl]pyrido-[3,2-*d*]pyrimidines is described. Nitration of 2,6-dichloropyridine provided the 3-nitro derivative which was converted to 6-chloro-3-nitro-2-pyridinecarbonitrile (V) with cuprous cyanide. Condensation of an aryl thiol with V gave the 6-arylthiopyridines VI which were reduced with iron in hydrochloric acid and condensed with chloroformamidine to give the 6-arylthiopyrido[3,2-*d*]pyrimidin-2,4-diamines X. Alternatively V was reduced to the amine VIII condensed with chloroformamidine and the resulting 6-chloropyrido[3,2-*d*]pyrimidine (IX) was treated with an arylthiol. Oxidation of X provided sulfinyl and sulfonyl analogs.

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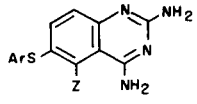
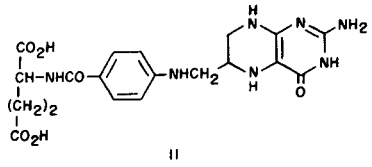
The potent antimalarial activity of the 2,4-diamino-6-[(aryl)thio]quinazolines (I) [3], led to the consideration of structures wherein the 2,4-diaminopyrido[3,2-*d*]pyrimidine



I

ring system was substituted for the 2,4-diaminoquinazoline moiety. This change might be expected to afford potential new antimetabolites whose architecture, physical properties, and chemical reactivity should more closely resemble the tetrahydrofolate coenzymes (II) [4] which are intimately involved in the biochemistry of the malaria parasite. We now report the synthesis and biological properties of a series of 2,4-diamino-6[(aryl)thio, sulfinyul and sulfonyl]pyrido[3,2-*d*]pyrimidines.



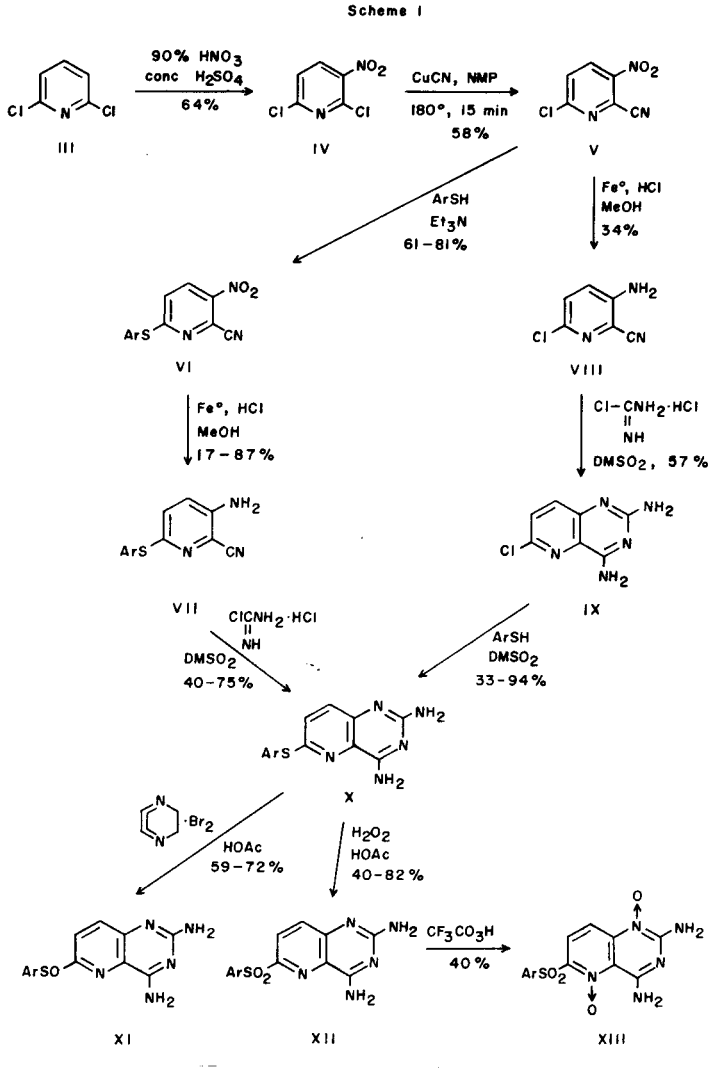
II

Tetrahydrofolic acid

Chemistry.

The 6-[(aryl)thio, sulfinyl, and sulfonyl]pyrido[3,2-*d*]pyrimidine-2,4-diamines X, XI, XII were prepared by the routes depicted in Scheme I. The nitration of 2,6-dichloropyridine (III) with 90% nitric acid in concentrated sulfuric acid gave 2,6-dichloro-3-nitropyridine (IV) [5] in 64% yield. Reaction with cuprous cyanide in *N*-methylpyrrolidone gave 6-chloro-3-nitro-2-pyridinecarbonitrile (V) in 58% yield. Several of the 6-[(aryl)thio]pyrido[3,2-*d*]pyrimidine-2,4-diamines were made by condensation of the appropriate arylthiol with V to give 6-arylthio-3-nitro-2-pyridinecarbonitriles, (VI, Table I, Procedures A and B). Reduction of VI with iron in hydrochloric acid gave the 3-amino-6-arylthio-2-pyridinecarbonitriles (VII, Table I, Procedures C and D) which were condensed with chloroformamidine hydrochloride to give the 6-arylthiopyrido[3,2-*d*]-pyrimidine-2,4-diamines (X, Table II, Procedure E).

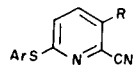
Scheme I



The remainder of the 6-[(aryl)thio]pyrido[3,2-*d*]pyrimid-

Table I

6-Arylthio-3-(amino,nitro)-2-pyridinecarbonitriles

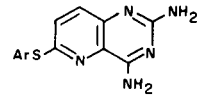


| No. | Ar | R | mp, °C | Purification Solvent | Procedure | Purified Yield, % | Formula | Analyses Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** [b] | 4-Cl-$C_6H_4$ | $NO_2$ | 97-104 | EtOH-$CCl_4$ | A | 62 | $C_{12}H_6ClN_3O_2S$ | | | [a] | | | |
| **2** | 4-Cl-$C_6H_4$ | $NH_2$ | 119-122 | $C_6H_{12}$-EtOAc | C | 42 | $C_{12}H_8ClN_3S$ | 55.07 | 54.79 | 3.08 | 3.06 | 16.05 | 16.05 |
| **3** [c] | 3-$CF_3$-$C_6H_4$ | $NO_2$ | 86-89 | EtOH | A | 61 | $C_{13}H_6F_3N_3O_2S$ | | | [a] | | | |
| **4** | 3-$CF_3$-$C_6H_4$ | $NH_2$ | 89.5-91 | $C_6H_{12}$-EtOAc | C | 63 | $C_{13}H_8F_3N_3S$ | 52.88 | 52.85 | 2.73 | 3.00 | 14.23 | 14.13 |
| **5** [d] | 4-($Me_2N$)-$C_6H_4$ | $NO_2$ | 140-143 | EtOH | A | 72 | $C_{14}H_{12}N_4O_2S$ | | | [a] | | | |
| **6** | 4-($Me_2N$)-$C_6H_4$ | $NH_2$ | 179-181.5 | 2-PrOH | C | 78 | $C_{14}H_{14}N_4S$ | 62.20 | 62.02 | 5.22 | 5.21 | 20.72 | 20.97 [f] |
| **7** [e] | 2-Naphthyl | $NO_2$ | 210-211.5 | EtOH | B | 81 | $C_{16}H_9N_3O_2S$ | 62.53 | 62.44 | 2.95 | 3.16 | 13.67 | 13.29 [g] |
| **8** | 2-Naphthyl | $NH_2$ | 124-125 | EtOH | D | 17 | $C_{16}H_{11}N_3S$ | 69.29 | 69.11 | 4.00 | 4.14 | 15.15 | 14.90 [h] |

[a] Not analyzed but of sufficient purity for use in next step. [b] The 4-chlorobenzenethiol was obtained from Aldrich Chemical Company and was used without purification. [c] The 3-(trifluoromethyl)benzenethiol was obtained from Pierce Chemical Company and was used without purification. [d] The 4-(dimethylamino)benzenethiol was obtained from Pitt Consol Company and was used without purification. [e] The 2-naphthalenethiol was obtained from Eastman Organic Chemicals Company and was used without purification. [f] S, Calcd: 11.86. Found: 11.94. [g] S, Calcd: 10.43. Found: 10.55. [h] S, Calcd. for 11.56. Found: 11.77.

Table II

6-[Arylthio]pyrido[3,2-*d*]pyrimidine-2,4-diamines



| No. | Ar | mp, °C | Purification Solvent | Procedure | Purified Yield, % | Formula | Analyses Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **9** [a] | 2,4,5-$Cl_3$-$C_6H_2$ | 308-310.5 | HOAc | F | 42 | $C_{13}H_8Cl_3N_5S$ | 41.90 | 41.76 | 2.16 | 2.53 | 18.79 | 18.83 |
| **10** [a] | 3,4-$Cl_2C_6H_3$ | 279-281 | DMF | F | 83 | $C_{13}H_9Cl_2N_5S$ | 46.17 | 45.98 | 2.68 | 2.76 | 20.17 | 20.52 |
| **11** | 4-Cl-$C_6H_4$ | 243-244.5 | 2-PrOH | E | 40 | $C_{13}H_{10}ClN_5S$ | 51.40 | 51.34 | 3.32 | 3.62 | 23.06 | 23.09 [c] |
| **12** [a] | 4-F-$C_6H_4$ | 247-248 | HOAc | F | 50 | $C_{13}H_{10}FN_5S$ | 54.34 | 54.01 | 3.50 | 3.70 | 24.38 | 24.58 |
| **13** | 3-$CF_3$-$C_6H_4$ | 210.5-212 | DMF | E | 52 | $C_{14}H_{10}F_3N_5S$ | 49.85 | 49.41 | 3.00 | 3.18 | 20.76 | 20.76 |
| **14** | 4-$Me_2N$-$C_6H_4$ | 227-231 | DMF | E | 48 | $C_{15}H_{16}N_6S$ | 57.67 | 57.34 | 5.16 | 5.20 | 26.90 | 27.36 |
| **15** [b] | 1-Naphthyl | 229-232 | HOAc | F | 33 | $C_{17}H_{13}N_5S$ | 63.93 | 63.49 | 4.10 | 4.14 | 21.92 | 21.76 |
| **16** | 2-Naphthyl | 240-242 | EtOH | E | 37 | $C_{17}H_{13}N_5S$ | 63.93 | 63.66 | 4.10 | 4.22 | 21.93 | 21.67 [d] |

[a] The 2,4,5-trichloro; 3,4-dichloro; and 4-fluorobenzenethiols were obtained from Aldrich Chemical Company and were used without purification. [b] The 1-naphthalenthiol was obtained from Eastman Organic Chemicals Company and was used without purification. [c] Cl, Calcd: 11.67. Found: 11.53. S, Calcd: 10.55. Found: 10.59. [d] S, Calcd: 10.04. Found: 10.09.

ine-2,4-diamines X were produced by initial reduction of 6-chloro-3-nitro-2-pyridinecarbonitrile (V) with iron and hydrochloric acid to give 3-amino-6-chloro-2-pyridinecarbonitrile (VIII) (34% yield) followed by condensation with chloroformamidine hydrochloride in dimethyl sulfone (Table II, Procedure F) to give IX and finally treatment with an arylthiol.

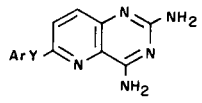
Oxidation of X with the bromine complex of 1,4-diazabicyclo[2.2.2]octane [6] gave the 6-[(aryl)sulfinyl]pyrido-[3,2-*d*]pyrimidine-2,4-diamines (XI, Table III, Procedure G). Similarly hydrogen peroxide in acetic acid gave the 6-[(aryl)sulfonyl]pyrido[3,2-*d*]pyrimidine-2,4-diamines (XII, Table III, Procedure H). In one case oxidation of 6-[(4-chlorophenyl)sulfonyl]pyrido[3,2-*d*]pyrimidine-2,4-diamine with peroxytrifluoroacetic acid gave a compound that is presumed to be the corresponding 1,5-dioxide (XIII, Table III, Procedure I).

Suppressive Antimalarial Screening in Mice.

The 2,4-diamino-6-[(aryl)thio, sulfinyl, and sulfonyl]-pyrido[3,2-*d*]pyrimidines **9-25** were tested against a normal drug-sensitive strain of *P. berghei* in mice by the

Table III

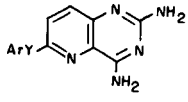
6-[(Aryl)sulfinyl and sulfonyl]pyrido[3,2-*d*]pyrimidine-2,4-diamines



| No. | ArY | mp, °C | Purification Solvent | Procedure | Purified Yield, % | Formula | Analyses Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found | Water, % Calcd. | Water, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **17** | 3,4-$Cl_2$-$C_6H_3$-SO | 260-263 | 2-PrOH | G | 72 | $C_{13}H_9Cl_2N_5OS$ | 44.08 | 44.01 | 2.56 | 2.60 | 19.77 | 19.58 | | |
| **18** | 4-F-$C_6$-$H_4$-SO | 213-215 | 2-PrOH-EtOH | G | 59 | $C_{13}H_{10}FN_5OS$ | 51.48 | 51.42 | 3.32 | 3.48 | 23.09 | 23.33 | | |
| **19** | 3-$CF_3$-$C_6H_4$-SO | 234-237 | EtOH | G | 64 | $C_{14}H_{10}F_3N_5OS \cdot 0.8\ H_2O$ | 45.73 | 45.59 | 2.18 | 2.28 | 19.05 | 19.09 | 3.92 | 3.88 |
| **20** | 3,4-$Cl_2$-$C_6H_3$-$SO_2$ | 313-315 | EtOAc-HOAc | H | 40 | $C_{13}H_9Cl_2N_5O_2S$ | 42.17 | 42.17 | 2.45 | 2.69 | 18.91 | 18.64 | | |
| **21** | 4-F-$C_6H_4$-$SO_2$ | 265-266 | MeOH | H | 36 | $C_{13}H_{10}FN_5O_2S$ | 48.90 | 48.72 | 3.16 | 3.24 | 21.93 | 21.70 | | |
| **22** | 3-$CF_3$-$C_6H_4$-$SO_2$ | 236-240 | EtOH | H | 69 | $C_{14}H_{10}F_3N_5O_2S$ 0.2 $C_2H_5OH$ | 45.69 | 45.44 | 2.98 | 3.06 | 18.49 | 18.69 | | |
| **23** | 2-Naphthyl-$SO_2$ | 258-260 | $H_2O$ Wash | H | 82 | $C_{17}H_{13}N_5O_2S \cdot 0.86\ H_2O$ | 55.65 | 55.94 | 3.89 | 3.72 | 19.09 | 19.07 | 4.22 | 4.24 |
| **24** | 4-Cl-$C_6H_4$-$SO_2$ | 270-272 | EtOH | H | 49 | $C_{13}H_{10}ClN_5O_2S$ 0.5 $H_2O$ | 45.29 | 45.28 | 3.22 | 3.21 | 20.31 | 20.41 | 2.61 | 2.58 |
| **25** | 4-Cl-$C_6H_4SO_2$ 1,5-Dioxide | 276 dec | HOAc | I | 40 | $C_{13}H_{10}ClN_5O_4S \cdot 0.7\ H_2O$ | 41.03 | 41.43 | 3.03 | 2.77 | 18.40 | 18.51 | 3.38 | 3.78 |

Table IV

Parenteral antimalarial effects of 6-[(aryl)thio,sulfinyl, sulfonyl] Pyrido[3,2-*d*]pyrimidine-2,4-diamines against *Plasmodium Berghi* in mice



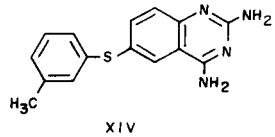
| Compound No. | △MST; T or C [a] single s.c. dose, mg/kg 640 | 320 | 160 | 80 | 40 | 20 | 10 |
|---|---|---|---|---|---|---|---|
| **9** | 1.3 | -- | 0.7 | -- | 0.5 | -- | -- |
| **10** | 9.7 | 6.9 | 5.6 | 2.1 | 1.0 | 0.5 | -- |
| **11** | -- | C2/5 | 15.1 | 12.5 | 11.3 | 4.1 | 1.9 |
| **12** | C5/5 | C4/5 | C3/12 | 15.1 | 12.7 | 3.3 | -- |
| **13** | 12.5 | 11.9 | 10.9 | 7.1 | 3.1 | 0.3 | -- |
| **14** | C5/5 | C10/10 | C10/10 | C7/10 | 11.6 | 9.0 | -- |
| **15** | C10/10 | C3/5 | C4/10 | 13.5 | 7.4 | 5.9 | -- |
| **16** | -- | C3/5 | C2/5 | C1/5 | 9.3 | 3.7 | 0.7 |
| **17** | T3/5 | -- | T2/5 | -- | T1/5 | -- | -- |
| **18** | T7/10 | 8.9 | 6.8 | 6.1 | 5.0 | 3.5 | -- |
| **19** | 13.5 | 11.7 | 9.1 | 4.9 | 1.0 | 0.3 | -- |
| **20** | 12.6 | 9.1 | 5.8 | 2.9 | 0.7 | 0.5 | -- |
| **21** | -- | C4/10 | C2/5 | C2/10 | 8.7 | 6.2 | -- |
| **22** | C6/15 | C4/10 | 9.6 | 5.5 | 3.6 | 1.3 | -- |
| **23** | 14.9 | 10.0 | 6.2 | 2.6 | 1.1 | 0.6 | -- |
| **24** | C10/10 | C5/5 | C4/10 | 12.7 | 12.1 | 4.9 | -- |
| **25** | -- | 10.2 | 6.1 | 4.7 | 2.9 | 1.3 | 0.1 |
| XIV | C5/5 | C10/10 | C10/10 | C10/10 | C10/10 | C10/10 | 10.7 |

[a] △MST 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 2-6 after injection which are attributed to drug action. C indicates the number of mice surviving at 60 days post infection and termed "cured", data to establish parasitological cure based on subinoculation are unavailable. Each entry at each dose level represents results with a 5-animal group.

parenteral route [7,8]. The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 hours postinfection. Extension of the mean survival time of the treated mice is interpreted as evidence of antimalarial activity [9].

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 mean survival time of infected control mice in the present study ranged from 6.1 to 6.3 days.

Antimalarial activity (Table IV) was demonstrated by several of the analogs, the most potent being the [4-(dimethylamino)phenyl]thio analog, Number 14. However this system was clearly of a lower order of activity than the corresponding 6-arylthioquinazolines as represented by XIV in Table IV.



XIV

Surprisingly, even oxidation to the sulfoxide of sulfone did not serve to improve the potency of the members of this series.

## EXPERIMENTAL

Melting points (uncorrected) were taken on a Thomas-Hoover capillary melting point apparatus. The $^1$H-nmr 90-MHz spectra were obtained with a Varian Associates EM-390 or Bruker B-NC-12 instrument.

2,6-Dichloro-3-nitropyridine (IV) [10].

To a solution of 90% nitric acid (900 ml) and concentrated sulfuric acid (1.5 ℓ) at 25° was added 2,6-dichloropyridine (300 g, 2.03 moles). The solution was heated to reflux over 40 minutes and maintained at reflux for 2.75 hours. The solution was cooled, poured onto ice and the solid collected to give 290.9 g of crude IV, mp 51-58°. Crystallization from 3.3 ℓ of 10:1 hexane-benzene gave 230.5 g of the product as cream needles, mp 60-63°, and a second crop (21.9 g) mp 55-58° (total yield 64.5%). Recrystallization of a 5 g portion of the first crop, from hexane, gave 4.31 g of IV, mp 62.5-63.5°.

*Anal.* Calcd. for $C_5H_2Cl_2N_2O_2$: C, 31.12; H, 1.05; N, 14.51. Found: C, 31.27; H, 1.27; N, 14.42.

6-Chloro-3-nitro-2-pyridinecarbonitrile (V).

A mixture of 2,6-dichloro-3-nitropyridine (100 g, 0.518 mole) and cuprous cyanide (92.8 g, 1.04 moles) in 1-methylpyrrolidinone was heated as rapidly as possible (18 minutes) to 180°, then maintained at 180 ± 2° with good stirring for 15 minutes. After cooling to 10° the deep brown solution was poured into chilled water (4 ℓ) and stirred for 30 minutes. The flocculent, brown precipitate, still containing bits of black tar, was collected on a Buchner funnel and washed well with water. After drying for about one hour, the moist solid was extracted three times with one liter portions of boiling benzene with good stirring for ten minutes each. The combined benzene extracts were washed three times with 500 ml portions of water then with 200 ml of saturated sodium chloride, and dried over magnesium sulfate. Concentration on a rotary evaporator in a 70° water bath gave 86 g of rose colored crystals which still contained a significant amount of solvent. This was slurried in 200 ml of an ether-petroleum ether (4:1) mixture and filtered to obtain 54.8 g (58%) of V as tan crystals, mp 107-115°.

Analysis (tlc, alumina-benzene) indicated the presence of impurities (at $R_f$ = 0.4 and 0.0) and the desired V ($R_f$ 0.6), however the purity proved sufficient for use in subsequent reactions.

3-Amino-6-chloro-2-pyridinecarbonitrile (VIII).

To a suspension of 4.0 g (0.0218 mole) of 6-chloro-3-nitropicolinonitrile in 15 ml of concentrated hydrochloric acid and 45 ml of methanol was added portionwise 4.27 g (0.0763 mole) of iron powder at a rate sufficient to maintain gentle reflux. When addition was complete the mixture was refluxed for an additional 0.5 hours and poured into 650 ml of water. Filtration of the resulting slurry gave 1.37 g of dull yellow solid mp 171.5-175°. The filtrate was made basic with concentrated ammonium hydroxide, the resulting slurry was filtered and both the solid and the filtrate were extracted with ether. The combined extracts were dried over magnesium sulfate and evaporated leaving 1.70 g of cream solid mp 158-168°. The combined solids were recrystallized from 95% ethanol to give 1.2 g (34%) of cream solid mp 175-176.5°.

*Anal.* Calcd. for $C_6H_4ClN_3$: C, 46.93; H, 2.62; N, 27.36; Cl, 23.08. Found: C, 47.10; H, 2.75; N, 27.52; Cl, 22.84.

6-Arylthio-3-nitro-2-pyridinecarbonitrile (VI), (**1**,**3**,**5**, Table I, Procedure A).

A slurry of potassium carbonate (6.9 g, 0.05 mole) and 6-chloro-3-nitro-2-pyridincarbonitrile (5.0 g, 0.0272 mole, V) in acetone (50 ml) was cooled in an ice bath and 4-(dimethylamino)benzenethiol was added at a rate sufficient to keep the temperature below 10°. The mixture was stirred with cooling for an additional 0.25 hour and poured into water. The solid that formed was washed with water and recrystallized from ethanol to give 6-[[4-(dimethylamino)phenyl]thio]-3-nitro-2-pyridinecarbonitrile (**5**) (5.9 g, 72%) mp 140-143°. This material was sufficiently pure for use in the next step. Compounds **1** and **3** were prepared by this method (Table I).

6-(2-Naphthylthio)-3-nitro-2-pyridinecarbonitrile (**7**), (Table I, Procedure B).

A slurry of 6-chloro-3-nitro-2-pyridinecarbonitrile (V) (5.0 g, 0.026 mole), 2-naphthalenethiol (4.34 g, 0.027 mole), triethylamine (2.73 g, 0.027 mole) and 2-ethoxyethanol (35 ml) was stirred and heated on a steam bath for 2.5 hours, then cooled and filtered. The resulting solid was washed with 95% ethanol to give **7** (6.75 g, 81%) as a bright yellow powder, mp 210-211.5°.

*Anal.* Calcd. for $C_{16}H_9N_3O_2S$: C, 62.53; H, 2.95; N, 13.67; S, 10.43. Found: C, 62.44; H, 3.16; N, 13.29; S, 10.55.

3-Amino-6-arylthio-2-pyridinecarbonitriles VII, (Compounds **2**, **4**, and **6**, Table I, Procedure C).

To a suspension of 6-[[4-(dimethylamino)phenyl]thio]-3-nitro-2-pyridinecarbonitrile (6.8 g, 0.0226 mole) in methanol (80 ml) and concentrated hydrochloric acid (25 ml) was added iron powder (5.06 g, 0.0905 g-atom) portionwise at a rate sufficient to maintain gentle reflux. When addition was complete the mixture was heated under reflux for an additional two hours and poured into water. The solution was made basic with concentrated ammonium hydroxide and the resulting solid was collected on celite. The celite mat was extracted with acetone, the organic solution was concentrated *in vacuo* and the residue was poured into water. The solid that formed was collected, washed with water and dried *in vacuo* to give 3-amino-6-[[4-(dimethylamino)phenyl]thio]-2-pyridinecarbonitrile (**6**) (5.3 g, 87%), mp 175-180°. Recrystallization of 1.0 g of this material from 2-propanol gave 0.9 g of **6**, mp 179-181.5°.

*Anal.* Calcd. for $C_{14}H_{14}N_4S$: C, 62.20; H, 5.22; N, 20.72; S, 11.86. Found: C, 62.02; H, 5.21; N, 20.97; S, 11.94.

Compounds **2** and **4** were also prepared by this method. Results appear in Table I.

3-Amino-6-(2-naphthylthio)-2-pyridinecarbonitrile (**8**), (Procedure D).

Solid 6-(2-naphthylthio)-3-nitro-2-pyridinecarbonitrile (**7**) (39.8 g, 0.13 mole) was added portionwise to a solution of stannous chloride dihydrate (73.3 g, 0.322 mole) in concentrated hydrochloric acid (200 ml) and glacial acetic acid (200 ml) over 0.5 hour. The mixture was stirred at room temperature for 26 hours and poured into ice water containing 50% sodium hydroxide (250 ml). The resulting solid was collected and extracted into acetone. The extract was concentrated to dryness and the residue was extracted with ether leaving 9.0 g of impure starting material. The ether extracts were filtered through florisil (100 g) and the solvent evaporated. The residue was extracted into methanol discarding 5.5 g of insoluble material. The solution was evaporated and the residue was dissolved in benzene and chromatographed on a 400 g florisil column eluting first with benzene and then with benzene-5% ethylacetate to give 11.3 g of light yellow solid. Recrystallization from anhydrous ethanol gave **8** (6.0 g, 17%) as a cream solid mp 124-125°.

*Anal.* Calcd. for $C_{16}H_{14}N_4S$: C, 69.29; H, 4.00; N, 15.15; S, 11.56. Found: C, 69.11; H, 4.14; N, 14.90; S, 11.77.

6-Chloropyrido[3,2-*d*]pyrimidine-2,4-diamine (IX).

A mixture of 3-amino-6-chloro-2-pyridinecarbonitrile (VIII) (1.1 g, 7.2 mmoles), chloroformamidine hydrochloride (1.7 g, 15 mmoles) and dimethylsulfone (4.5 g) was heated in an oil bath at 165°. After heating for ten minutes the internal temperature was 190° and the hot mixture was poured into water. The aqueous solution was filtered to remove a small amount of insoluble material and made basic with 10% sodium hydroxide. The solid that formed was collected, washed with water and dried *in vacuo* to give the product as a hemihydrate (0.8 g, 57%) mp 248-251.5°.

*Anal.* Calcd. for $C_9H_6ClN_5 \cdot 0.5H_2O$: C, 41.09; H, 3.45; N, 34.23; $H_2O$, 4.40. Found: C, 40.83; H, 3.75; N, 34.32; $H_2O$, 4.65.

6-[(Aryl)thio]pyrido[3,2-*d*]pyrimidine-2,4-diamines (X), (Table II, Procedure E).

A finely ground mixture of 3-amino-6-[[4-(dimethylamino)phenyl]thio]-2-pyridinecarbonitrile [6] (4.30 g, 0.0159 mole), chloroformamidine hydrochloride (3.66 g, 0.0318 mole) and dimethylsulfone (17 g) was heated in an oil bath at 150°. The internal temperature quickly rose to 152° and then slowly fell to 145° over 0.75 hour. The oil bath temperature was then raised to 165° and heating was continued for a total of 1.5 hours. The hot mixture was poured into 500 ml of water and the solution was filtered to remove a small amount of fine solid. The filtrate was made basic with 10% sodium hydroxide and the resulting solid was collected. Washing with water and then with acetone gave 6-[[4-(dimethylamino)-

phenyl]thio]pyrido[3,2-*d*]pyrimidine-2,4-diamine (**14**) (4.5 g, 85%) as a yellow powder, mp 227-231°. Recrystallization from DMF gave 3.75 g of yellow solid that melted at 212-217° with effervescence, resolidified, and remelted at 227-232°. This solid was dissolved in 200 ml of 1*N* hydrochloric acid and poured into excess dilute sodium hydroxide. The resulting solid was collected, washed with water, then with acetone and dried *in vacuo* to give **14** (2.4 g, 48%) mp 227-231°.

*Anal.* Calcd. for $C_{15}H_{16}N_6S$: C, 57.67; H, 5.16; N, 26.90. Found: C, 57.34; H, 5.20; N, 27.36.

Compounds **11**, **13**, and **16** were prepared by this method (Table II).

Procedure F.

A mixture of 6-chloropyrido[3,2-*d*]pyrimidine-2,4-diamine (IX) (5.0 g, 0.0265 mole), 4-fluorobenzenethiol (3.8 g, 0.030 mole) and dimethylsulfone (20 g) was heated at 195° for one hour. The hot mixture was triturated with water, and the resulting solid was collected, washed with water and dissolved in DMF. The solution was poured into dilute sodium hydroxide and the solid that formed was collected. The original aqueous filtrate and washings were made basic with dilute sodium hydroxide and the solid that formed was collected. The combined solids were washed with boiling acetone, and then with ether to give 6-[(4-fluorophenyl)thio]-pyrido[3,2-*d*]pyrimidine-2,4-diamine (**12**) (4.7 g, 94%) mp 246-247°. Crystallization of 1.5 g of this material from glacial acetic acid followed by washing first with acetone and then with ether, and drying *in vacuo* gave **12** (0.8 g) mp 247-248°.

*Anal.* Calcd. for $C_{13}H_{10}FN_5S$: C, 54.34; H, 3.50; N, 24.38. Found: C, 54.01; H, 3.70; N, 24.58.

Compounds **9**, **10**, and **15** were also prepared in this manner (Table II).

6-[(Aryl)sulfinyl]pyrido[3,2-*d*]pyrimidine-2,4-diamines (XI), (Procedure G).

A mixture of 6-[(4-fluorophenyl)thio]pyrido[3,2-*d*]pyrimidine-2,4-diamine (**12**) (1.9 g, 6.62 mmoles) and the bromine complex of 1,4-diazabicyclo[2.2.2]octane (1.3 g, 3.1 mmoles) in 70% acetic acid (100 ml) was stirred at room temperature for 19 hours. The resulting solution was poured into ice water containing 90 g of 50% sodium hydroxide. The solid that formed was collected, washed with water and crystallized from 2-propanol. The resulting solid was recrystallized from ethanol to give 6-[(4-fluorophenyl)sulfinyl]pyrido[3,2-*d*]pyrimidine-2,4-diamine (**18**) (1.1 g, 59%) mp 213-215°.

*Anal.* Calcd. for $C_{13}H_{10}FN_5OS$: C, 51.48; H, 3.32; N, 23.09. Found: C, 51.42; H, 3.48; N, 23.33.

Compounds **17** and **19** were prepared in this manner (Table III).

6-[(Aryl)sulfonyl]pyrido[3,2-*d*]pyrimidine-2,4-diamines (XII), Procedure H.

A suspension of 6-[(4-fluorophenyl)thio]pyrido[3,2-*d*]pyrimidine-2,4-diamine (**18**) (2.0 g, 6.96 mmoles), acetic acid (50 ml) and 30% hydrogen peroxide (18 ml, 0.18 mole) was stirred at room temperature for 41 hours. The resulting solution was poured into excess dilute sodium hydroxide and the solid that formed was collected. This solid was washed with water and extracted into acetone, the extracts were concentrated to dryness and the residue was triturated with ether to give 6-[(4-fluorophenyl)sulfonyl]pyrido[3,2-*d*]pyrimidine-2,4-diamine (**21**) (1.7 g, 76%) mp 261-263°. Recrystallization from methanol (200 ml) gave **21** (0.8 g, 36%) as light orange crystals, mp 265-266°.

*Anal.* Calcd. for $C_{13}H_{10}FN_5O_2S$: C, 48.90; H, 3.16; N, 21.93. Found: C, 48.72; H, 3.24; N, 21.70.

Compounds **20**, **22**, **23**, and **24** (Table III) were prepared by this method.

6-[(4-Chlorophenyl)sulfonyl]pyrido[3,2-*d*]pyrimidine-2,4-diamine 1,5-Dioxide (XIII, 25), (Procedure I).

An ice cold mixture of 30% hydrogen peroxide (0.6 ml, 6.0 mmoles) in dichloromethane (15 ml) was treated dropwise with trifluoroacetic anhydride (2.3 ml , 16 mmoles). When addition was complete 6-[(4-chlorophenyl)sulfonyl]pyrido[3,2-*d*]pyrimidine-2,4-diamine (**24**) (1.0 g, 3.0 mmoles) was added and the resulting solution was allowed to stir at room temperature for 21 hours. The solution was evaporated, by passing a steam of nitrogen over the surface, and water was added to the residue. The solid that formed was collected, washed with water, and then with boiling acetone to give **25** (0.45 g, 40%) as an orange-brown solid 0.7 hydrate, mp 276° dec.

*Anal.* Calcd. for $C_{13}H_{10}ClN_5O_4S \cdot 0.7H_2O$: C, 41.03; H, 3.03; N, 18.40; $H_2O$, 3.38. Found: C, 41.43; H, 2.77; N, 18.61; $H_2O$, 3.78.

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

[10] Care should be taken in handling II as our experience has shown it to be a potent vesicant.