Synthesis of Potential Antimalarial Agents. VII. Azaquinolines. I. The Preparation of Some Pteridines and Pyrido[3,4-*b*]pyrazines (1)

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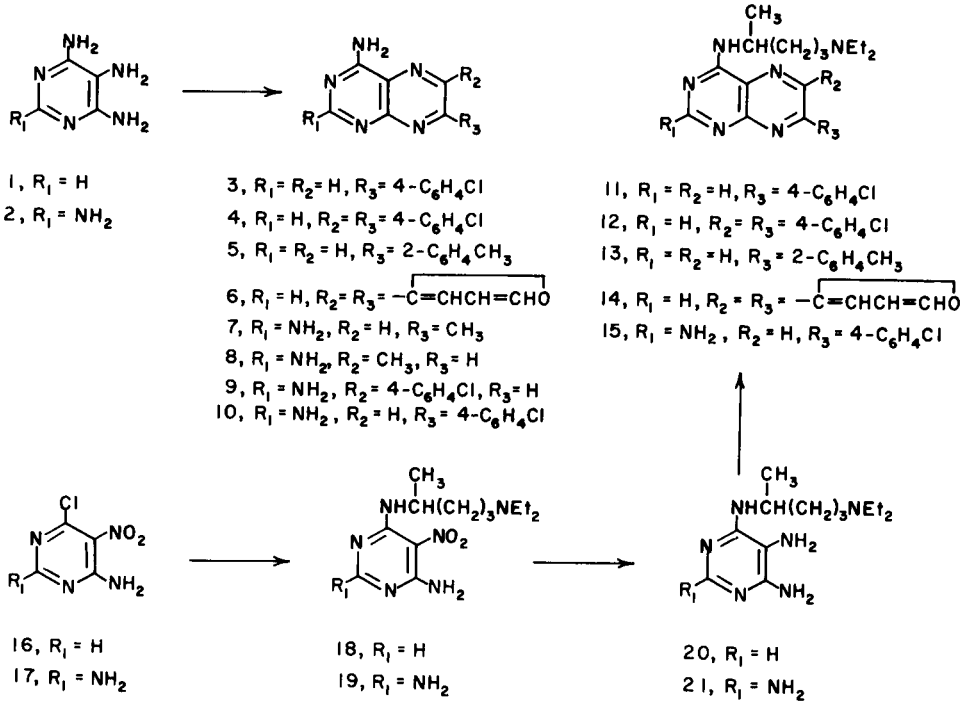
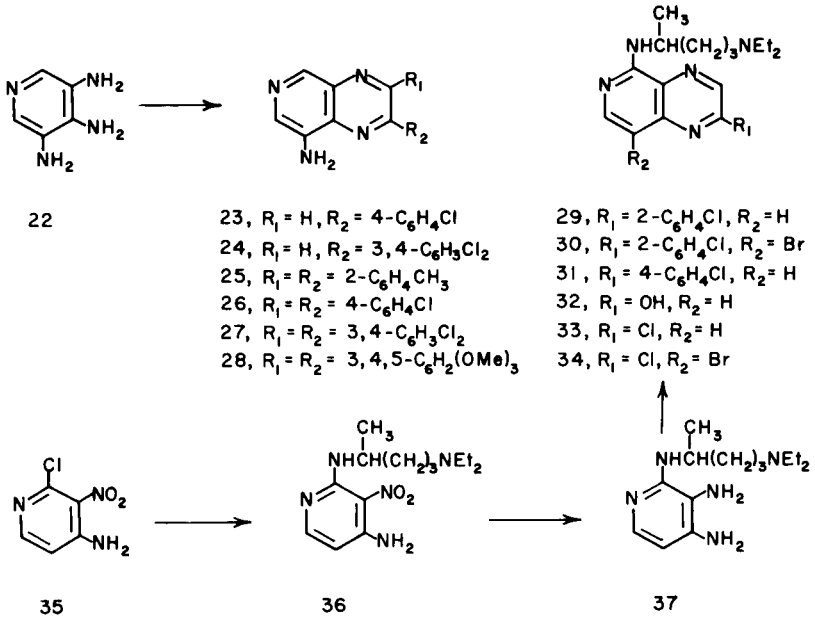
In previous papers of this series we reported that some derivatives of the pyrido[2,3-*b*]pyrazine ring system cured mice infected with *Plasmodium berghei* (2). This paper reports the search for antimalarial drugs of new structural types in the pteridine and pyrido[3,4-*b*]pyrazine ring systems.

The condensation of 4,5,6-triaminopyrimidine (**1**) with *p*-chlorophenylglyoxal, 4,4′-dichlorobenzil, *o*-tolylglyoxal, and 2-furil, respectively, gave the 4-aminopteridines **3-6**. In the glyoxal reactions the product was assigned to the 7-substituted rather than the 6-substituted pteridine since this type reaction invariably gives mainly the 7-isomer (3,4). Further, the pmr spectra indicated that the purified products were homogeneous. The condensation of 2,4,5,6-tetraaminopyrimidine (**2**) with methylglyoxal by the reported procedure gave the 7-methylpteridine **7** (3). In the presence of the carbonyl binding reagent, sodium bisulfite, this reaction provided the 6-methylpteridine **8** (3). Similarly treatment of **2** with *p*-chlorophenylglyoxal, either with or without sodium bisulfite, gave the 6- and 7-(*p*-chlorophenyl)pteridines **9** and **10**. Both reactions gave mixtures of the two isomers from which the major isomer was obtained by recrystallization.

The 4-[[4-(diethylamino)-1-methylbutyl]amino]pteridines (**11-14**) were prepared by treatment of **16** (5) with 2-amino-5-diethylaminopentane to give **18**, reduction of the nitro group of **18** with Raney nickel to give **20**, and condensation of the latter with the appropriate glyoxal or benzil. Similarly the preparation of the pteridine analog (**15**) of an active pyrido[2,3-*b*]pyrazine (2) was carried out by the reaction sequence **17** (6), **19**, **21**, **15**.

The 8-aminopyrido[3,4-*b*]pyrazines (**23-28**) were prepared by the condensation of 3,4,5-triaminopyridine (**22**) (7) with various glyoxals and benzils. In the glyoxal reactions the structural assignments are based on previous work, which indicated that the major isomer resulted from the condensation of the aldehyde carbonyl moiety of the glyoxal with the 3-amino rather than the 4-amino group





of a 3,4-diaminopyridine (8).

To prepare the 5-[[4-(diethylamino)-1-methylbutyl]-amino[pyrido[3,4-*b*]pyrazines (**29-34**), 2-chloropyridine was converted to **35** in three steps by the reported procedure (9). Reaction of **35** with 2-amino-5-diethylaminopentane gave a 74% yield of **36** as an analytically pure oil. Reduction of the nitro group of **36** with Raney nickel gave **37**, which was isolated as the trihydrochloride. The condensation of **37** with *o*- and *p*-chlorophenylglyoxals and ethyl glyoxylate, respectively, gave **29**, **31**, and **32**. The bromination of **29** *meta* to the pyridine ring nitrogen occurred readily to give **30** (10). The chlorodehydroxylation of **32** with phosphorus oxychloride gave the chloroquine analog **33**. This compound was also brominated to give **34**.

Compounds were tested against lethal, blood induced *Plasmodium berghei* infections in mice (11). None of the compounds showed significant antimalarial activity. The test results obtained with the pteridine **15** and its active 3-deaza analog (2) indicated that the addition of the ring nitrogen to the latter to give the former resulted in loss of activity while toxicity was retained. Further the activity of the pyrido[2,3-*b*]pyrazines (2) and the inactivity of the pyrido[3,4-*b*]pyrazines (**29-34**) suggested that activity might depend on the side chain being *para* to the ring nitrogen as in chloroquine.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus. The ultraviolet absorption spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer, whereas the infrared absorption spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 521 spectrophotometer. The pmr spectra were determined with a Varian A-60A spectrometer at a probe temperature of about 40° using tetramethylsilane as an internal reference. The relative peak areas are given to the nearest whole number. Silica gel H was obtained from Brinkmann Instruments, Inc. and Raney Active Catalyst No. 28 from W. R. Grace & Co.

4-Amino-7-(*p*-chlorophenyl)pteridine Monohydrate (**3**).

A suspension of **1** sulfate hydrate (2.41 g., 10.0 mmoles) in water (40 ml.) was treated with a solution of barium chloride dihydrate (2.44 g., 10.0 mmoles) in water (10 ml.). The mixture was heated for 10 minutes, cooled to room temperature, and filtered. The residue was washed with water (10 ml.), and the combined filtrate and wash was diluted to 120 ml. with water. To this solution was added sodium bicarbonate (1.68 g., 20.0 mmoles) followed by a solution of *p*-chlorophenylglyoxal monohydrate (1.87 g., 10.0 mmoles) in dioxane (30 ml.). The resulting mixture was stirred at room temperature for 1 hour, then heated at reflux for 1 hour. The mixture was filtered hot, and the solid was washed with water (3 x 10 ml.) and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 2.07 g. (80%); m.p. 308-310° dec.; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 232 (17.9), 257 (15.9), 358 (25.0)); *p*H 7–236 (19.7), 354 (15.4); 0.1 *N* sodium hydroxide, 237 (19.5), 354 (15.1); $\bar{\nu}$ in cm^{-1}: 3460, 3275, 1640 (NH); pmr (5% trifluoroacetic acid w/v), δ, 7.97 q (4, C_6H_4), 9.01, 9.57 (1, 1, 2-H, 6-H).

Anal. Calcd. for $C_{12}H_8ClN_5 \cdot H_2O$: C, 52.28; H, 3.66; Cl, 12.86; N, 25.40. Found: C, 52.40; H, 3.01; Cl, 13.27; N, 25.49.

4-Amino-6,7-bis(*p*-chlorophenyl)pteridine (**4**).

To a solution of **1** prepared as described above was added a solution of 4,4′-dichlorobenzil (2.79 g., 10.0 mmoles) in hot dioxane (30 ml.). The resulting mixture was heated at reflux for 10 hours, and the curde product (2.70 g.), contaminated with 4,4′-dichlorobenzil, was collected by filtration. Purification of this solid by recrystallization from dioxane-water or from ethanol was unsuccessful. The pure product was obtained by sublimation

of the contaminant at 140° *in vacuo*, yield 1.57 g. (42%); m.p. 295-296°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 233 (3.1), 262 (sh), 289 (15.8), 377 (17.1); *p*H 7–232 (2.2), 285 (17.8), 371 (13.2); 0.1 *N* sodium hydroxide, 232 (2.5), 286 (17.2), 371 (12.8); $\bar{\nu}$ in cm^{-1}: 3435, 3290, 1635 (NH).

Anal. Calcd. for $C_{18}H_{11}Cl_2N_5$: C, 58.71; H, 3.01; Cl, 19.26; N, 19.02. Found: C, 58.97; H, 3.20; Cl, 19.50; N, 19.10.

4-Amino-7-*o*-tolylpteridine (**5**).

To a solution of **1** prepared as described above, diluted to 165 ml. with water, was added a solution of an excess of impure *o*-tolylglyoxal hydrate (6.6 g.) in dioxane (30 ml.). The resulting mixture was heated at reflux for 3 hours, then filtered hot. This solid was washed with hot water (3 x 25 ml.) and ethanol (2 x 25 ml.) and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 2.9 g. (120%) of a product contaminated with *o*-tolylglyoxal. The crude product was recrystallized from boiling ethanol (75 ml.) and dried 4 hours at 100° *in vacuo* over phosphorus pentoxide, yield 1.1 g. (48%); m.p. 231-233°; λ max nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 350 (16.3); *p*H 7–344 (11.2); 0.1 *N* sodium hydroxide, 344 (10.9); $\bar{\nu}$ in cm^{-1}: 3460, 3270, 1625 (NH); pmr (5% trifluoroacetic acid w/v), δ, 2.59 (3, CH_3), 7.57 m (4, C_6H_4), 9.04, 9.34 (1, 1, 2-H, 6-H).

Anal. Calcd. for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 65.98; H, 4.91; N, 29.47.

4-Amino-6,7-bis(2-furyl)pteridine Monohydrate (**6**).

To a solution of **1** prepared as described above was added a warmed solution of 2-furil (1.90 g., 10.0 mmoles) in dioxane (40 ml.). The resulting solution was heated at reflux for 3 hours, and the crude product (1.8 g., 63%) was collected by filtration and washed with water (3 x 15 ml.) and ethyl ether (15 ml.). The product was recrystallized from methanol (125 ml.), yield 1.3 g. (44%); m.p. 216-218°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 287 (20.1), 350 (11.0), 418 (15.3); *p*H 7–243 (17.6), 291 (20.2), 401 (13.7); 0.1 *N* sodium hydroxide, 243 (17.6), 292 (19.9), 401 (13.5); $\bar{\nu}$ in cm^{-1}: 3560, 3430, 3290, 3210, 3110, 1670, 1630 (NH).

Anal. Calcd. for $C_{14}H_9N_5O_2 \cdot H_2O$: C, 56.57; H, 3.73; N, 23.56. Found: C, 56.83; H, 3.80; N, 23.42.

2,4-Diamino-6-(*p*-chlorophenyl)pteridine (**9**).

A mixture of **2** sulfate (10.9 g., 40 mmoles) and 98% sodium sulfite (119 g., 92 mmoles) in water (360 ml.) was heated and stirred at 60° until the solids dissolved. This solution was cooled to room temperature and a mixture of *p*-chlorophenylglyoxal monohydrate (7.5 g., 40 mmoles) and sodium bisulfite (2.0 g., 19 mmoles) in dioxane (40 ml.) was added. The resulting mixture was stirred 1 hour at room temperature, diluted with water (1200 ml.), and the resulting solution reduced in volume to 500 ml. by evaporation at reduced pressure. The solid that formed was collected by filtration, washed with water (3 x 100 ml.), and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 8.1 g. (74%) of a mixture of the 6- and 7-(*p*-chlorophenyl) isomers. The product (7.5 g.) was dissolved in hot 40% acetic acid (1160 ml.), filtered, and diluted with an equal volume of water. The solid that deposited was collected by filtration and dried *in vacuo* over phosphorus pentoxide at 100° for 4 hours, yield 2.1 g. (19%); m.p. 350°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 256 (11.0), 284 (9.0), 360 (25.9); *p*H 7–270, 384; 0.1 *N* sodium hydroxide, 271, 387; $\bar{\nu}$ in cm^{-1}: 3435, 3320, 3140, 1615 (NH); pmr (5% trifluoroacetic acid w/v), δ, 7.93 q (4, C_6H_4), 9.28 (1, 7-H).

Anal. Calcd. for $C_{12}H_9ClN_6$: C, 52.85; H, 3.33; Cl, 13.00; N, 30.82. Found: C, 52.63; H, 3.41; Cl, 13.35; N, 30.66.

2,4-Diamino-7-(*p*-chlorophenyl)pteridine Monohydrochloride (**10**).

A slurry of **2** sulfate (10.9 g., 40 mmoles) in 0.25 *N* hydrochloric acid, (800 ml.) was heated with stirring at 40° until the solid had dissolved. A solution of *p*-chlorophenylglyoxal monohydrate (7.5 g., 40 mmoles) in dioxane (40 ml.) was added, and the resulting mixture was heated at 40° for 1 hour. The mixture was then chilled in an ice bath and treated with 50% sodium hydroxide (52 g.). The solid that formed was collected by filtration, washed with water (3 x 250 ml.), then with acetone, and dried at room temperature *in vacuo* over phosphorus pentoxide; yield 8.5 g. (78%) of a mixture of the 6- and 7-(*p*-chlorophenyl) isomers. Recrystallization from hot 30% acetic acid (2 l.) gave a product (4.1 g.) containing more of 7-(*p*-chlorophenyl) isomer. This solid was triturated in boiling 1 *N* hydrochloric acid (3 x 400 ml.) and dried for 4 hours at 100° *in vacuo* over phosphorus pentoxide, yield 3.5 g. (28%); m.p. above 350°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 269 (30.6), 365 (12.1); *p*H 7–278, 388; 0.1 *N* sodium hydroxide, 279, 390; $\bar{\nu}$ in cm^{-1}: 3270, 3120, 1680, 1655, 1635 (NH); pmr (<2.5% trifluoroacetic acid w/v), δ, 7.88 q (4, C_6H_4), 9.40 (1, 6-H).

Anal. Calcd. for $C_{12}H_9ClN_6 \cdot HCl$: C, 46.62; H, 3.26; Cl, 22.94; N, 27.18. Found: C, 46.41; H, 3.39; Cl, 23.26; N, 27.31.

4-[[4-(Diethylamino)-1-methylbutyl]amino]-7-(*p*-chlorophenyl)-pteridine Monohydrochloride (**11**).

A solution of **18** hydrochloride (3.33 g., 10.0 mmoles) in water (250 ml.) was hydrogenated at atmospheric pressure in the presence of 5% palladium-on-charcoal catalyst (1.5 g.). The theoretical amount of hydrogen was adsorbed within 2 hours. The catalyst was removed by filtration (Celite), and the residue was washed with hot water (3 x 50 ml.). To the combined filtrate and washings was added a solution of *p*-chlorophenylglyoxal monohydrate (1.87 g., 10.0 mmoles) in dioxane (30 ml.). The resulting solution was heated at reflux for 3 hours, filtered hot, and the filtrate was evaporated to dryness at reduced pressure. This residue was dried azeotropically with ethanol, then repeatedly dissolved in 2-propanol, and reevaporated to dryness until the residue solidified. The resulting solid was triturated in 2-propanol (2 x 20 ml.), collected by filtration, and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 2.5 g. The crude product was recrystallized from boiling dioxane (250 ml.), yield 2.06 g. (47%); m.p. 201-202° dec.; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 238 (17.9), 258 (17.6), 367 (29.6), 378 (28.6); *p*H 7–233 (22.2), 260 (14.5), 282 (12.3), 317 (9.0), 370 (17.3); 0.1 *N* sodium hydroxide, 234 (23.1), 260 (14.5), 284 (12.5), 318 (8.9), 372 (17.2); $\bar{\nu}$ in cm^{-1}: 3430, 3375 (NH); pmr (5% trifluoroacetic acid w/v), δ, 7.90 m (4, C_6H_4), 8.90, 9.45 (1, 1, 2-H, 6-H).

Anal. Calcd. for $C_{21}H_{27}ClN_6 \cdot HCl$: C, 57.93; H, 6.48; N, 19.30. Found: C, 57.75; H, 6.56; N, 19.11.

6,7-Bis(*p*-chlorophenyl)-4-[[4-(diethylamino)-1-methylbutyl]-amino]pteridine Hydrochloride (**12**).

To a hot solution of 4,4′-dichlorobenzil (1.5 g., 5.0 mmoles) in ethanol (250 ml.) under nitrogen was added a solution of **20** 2.5 hydrochloride (1.8 g., 5.0 mmoles) in ethanol (50 ml.), and the whole was refluxed for 6 hours. After the addition of sodium bicarbonate (0.63 g., 7.5 mmoles) the reaction mixture was heated for an additional 0.5 hours. The yellow solid that deposited on cooling was collected by filtration and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 0.70 g. (47% recovery)

of unreacted 4,4'-dichlorobenzil; m.p. 199-201°. The filtrate was evaporated to dryness, suspended in water (20 ml.), and extracted with chloroform (5 x 10 ml.). The chloroform extracts were combined, evaporated to dryness, and the resulting residue was triturated with ethyl acetate and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 0.60 g. (23%); m.p. 204-206°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 234 (11.3), 293 (5.7), 384 (8.6); *p*H 7–233 (13.1), 290 (6.4), 381 (6.6); 0.1 *N* sodium hydroxide, 234 (12.2), 297 (7.7), 388 (6.1); $\bar{\nu}$ in cm^{-1}: 3420 (NH); 1580, 1570, 1560, 1535 (C=C, C=N).

Anal. Calcd. for $C_{27}H_{30}Cl_2N_6$·HCl: C, 59.40; H, 5.72; Cl, 19.48; N, 15.39. Found: C, 59.56; H, 5.76; Cl, 19.3; N, 15.42.

4-[[4-(Diethylamino)-1-methylbutyl]amino]-7-*o*-tolylpteridine Dihydrochloride (**13**).

A solution of **18** hydrochloride (3.33 g., 10.0 mmoles) in water (250 ml.) was hydrogenated at atmospheric pressure in the presence of 5% palladium-on-charcoal catalyst (1.5 g.). The theoretical amount of hydrogen was adsorbed within 1.5 hours. The catalyst was removed by filtration (Celite), and the residue was washed with hot water (3 x 50 ml.). To the combined filtrate and washings was added a solution of *o*-tolylglyoxal (2.36 g., 15.0 mmoles) in dioxane (15 ml.). The resulting mixture was heated at reflux for 2 hours and evaporated to dryness at reduced pressure. The residue was extracted with ethyl acetate (3 x 500 ml.), and the extracts were combined and evaporated to dryness. The residue (3.0 g.) was dissolved in 2-propanol (25 ml.), treated with an equivalent amount of concentrated hydrochloric acid (0.61 ml., 7.3 mmoles), and the resulting solution was evaporated to dryness. The residue was then triturated in dioxane (2 x 50 ml.), and the insoluble solid was collected and dried at 100° for 4 hours *in vacuo* over phosphorus pentoxide, yield 2.7 g. (60%); m.p. 238-240° dec.; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 234 (18.2), 358 (21.0), 372 (sh); *p*H 7–227 (22.0), 253 (10.7), 276 (8.1), 363 (13.5); 0.1 *N* sodium hydroxide, 227 (22.9), 252 (10.7), 276 (8.2), 364 (13.4); $\bar{\nu}$ in cm^{-1}: 3430, 1620 (NH); pmr (10% DMSO-d_6 w/v), δ, 7.53 m (4, C_6H_4), 8.93, 9.25 (1, 1, 2-H, 6-H).

Anal. Calcd. for $C_{22}H_{30}N_6$·2HCl: C, 58.53; H, 7.15; Cl, 15.71; N, 18.62. Found: C, 58.41; H, 7.26; Cl, 15.61; N, 18.47.

4-[[4-(Diethylamino)-1-methylbutyl]amino]-6,7-bis(2-furyl)pteridine Five-fourths Hydrochloride Hydrate (**14**).

A solution of **18** monohydrochloride (3.33 g., 10.0 mmoles) in 95% aqueous ethanol (250 ml.) was hydrogenated at atmospheric pressure in the presence of 5% palladium-on-charcoal catalyst (1.5 g.). The catalyst was removed by filtration (Celite) and washed with 95% aqueous ethanol (4 x 50 ml.). The combined filtrate and washings was heated to reflux under nitrogen, and a warm solution of 2-furil (1.90 g., 10.0 mmoles) in dioxane (30 ml.) was added. The resulting solution was heated at reflux for 6 hours, cooled, and evaporated to dryness *in vacuo*. The residue was triturated in water (300 ml.), and unreacted 2-furil (0.7 g.) was removed by filtration. The filtrate was reduced in volume to 50 ml., treated with 1 *N* sodium hydroxide (7.5 ml.), and extracted with chloroform (3 x 80 ml.). The combined extracts were evaporated to dryness, and the residue (2.90 g., 6.9 mmoles) was purified by column chromatography (silica gel H, chloroform eluent). The fractions containing the desired product were evaporated to dryness, treated with 1 *N* hydrochloric acid in ethanol, and reevaporated to dryness. The resulting residue was triturated in ethyl acetate, collected by filtration, and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 1.5 g. (32%); m.p. decomposes without melting from 110°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 288 (19.0), 308 (15.4), 422 (17.7); *p*H 7–243 (18.8), 308 (18.4), 410 (16.0); 0.1 *N* sodium hydroxide, 242 (18.9), 309 (18.0), 410 (16.0); $\bar{\nu}$ in cm^{-1}: 3400, 1610 (NH); 1580, 1555, 1525 (C=C, C=N).

Anal. Calcd. for $C_{23}H_{28}N_6O_2$·5/4HCl·H_2O: C, 57.06; H, 6.51; N, 17.36. Found: C, 57.20; H, 6.44; N, 17.44.

A portion of this sample was dried *in vacuo* over phosphorus pentoxide at 78°.

Anal. Calcd. for $C_{23}H_{28}N_6O_2$·5/4HCl·1/2H_2O: C, 58.15; H, 6.42; Cl, 9.33; N, 17.69. Found: C, 58.44; H, 6.49; Cl, 9.29; N, 17.60.

2-Amino-7-(*p*-chlorophenyl)-4-[[4-(diethylamino)-1-methylbutyl]amino]pteridine Dihydrochloride (**15**).

A suspension of **19** monohydrochloride monohydrate (2.40 g., 6.57 mmoles) in ethanol (100 ml.) was hydrogenated over Raney nickel catalyst (~5 g.) in a Parr shaking apparatus at an initial hydrogen pressure of 3.5 kg.-cm^{-2}. The catalyst was removed by filtration under nitrogen, and the colorless filtrate was treated with solid *p*-chlorophenylglyoxal monohydrate (1.90 g., 10.2 mmoles). The resulting orange solution was stirred at room temperature for 18 hours, refluxed under nitrogen for 30 minutes, cooled, and evaporated *in vacuo* to a dark red gum. This residue was dissolved in water (150 ml.), and the solution was adjusted to *p*H 10 with 50% sodium hydroxide. The mixture was extracted with chloroform (2 x 150 ml.), and the combined extracts were washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residual glass, shown to be a complex mixture by thin-layer chromatography, was dissolved in chloroform and poured onto a silica gel H column (200 g.) which had been poured and prewashed with chloroform. Elution with chloroform-methanol (9:1) gave three major zones; the middle band, containing the desired product, was collected and evaporated to dryness. This residue was dissolved in warm ethanol, and the resulting solution was treated with charcoal and acidified (*p*H 1) with 3.3 *N* ethanolic hydrochloric acid. Dilution of this solution with ethyl ether (500 ml.) precipitated a soft yellow solid which was collected by filtration and reprecipitated from dry ethanol (100 ml.) with ethyl ether to give an extremely hygroscopic yellow powder. This was collected by filtration under nitrogen and dried *in vacuo* over phosphorus pentoxide at 78°, yield 1.71 g. (53%); m.p. indefinite, sinters and decomposes slowly above 153°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 265 (10.3), 363 (28.7), 373 (sh); *p*H 7–276 (19.9), 385 (16.4); 0.1 *N* sodium hydroxide, 276 (19.9), 391 (16.2); $\bar{\nu}$ in cm^{-1}: 1650 (NH_2); 1610, 1545 (C=C, C=N); pmr (7.5% DMSO-d_6 w/v), δ, 7.95 (4, C_6H_4), 9.26 (1, 6-H).

Anal. Calcd. for $C_{21}H_{28}ClN_7$·2HCl: C, 51.80; H, 6.21; Cl, 21.85; N, 20.14. Found: C, 51.66; H, 6.44; Cl, 21.83; N, 20.25.

4-Amino-6-[[4-(diethylamino)-1-methylbutyl]amino]-5-nitropyrimidine Monohydrochloride (**18**).

A mixture of 2-amino-5-diethylaminopentane (3.2 g., 20 mmoles) and **16** (3.5 g., 20 mmoles) in ethanol (250 ml.) was refluxed for 1 hour under nitrogen and cooled to room temperature. The solid that deposited was collected by filtration and dried at 78° for 3 hours *in vacuo* over phosphorus pentoxide, yield 5.0 g. (75%); m.p. 131-133° dec.; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 241 (24.7), 294 (3.7), 341 (7.0); *p*H 7–345 (9.8); 0.1 *N* sodium hydroxide, 347 (9.6); $\bar{\nu}$ in cm^{-1}: 3385, 3330, 1635 (NH); 1580, 1540, 1520 (C=C, C=N).

Anal. Calcd. for $C_{13}H_{24}N_6O_2$·HCl: C, 46.91; H, 7.57; Cl, 10.65; N, 25.25. Found: C, 46.92; H, 7.66; Cl, 10.64; N, 25.08.

4,5-Diamino-6-[[4-(diethylamino)-1-methylbutyl]amino]pyrimidine Hydrochloride (2:5) (**20**).

A solution of **18** monohydrochloride (5.0 g., 15 mmoles) in 95% aqueous ethanol (200 ml.) was hydrogenated at atmospheric pressure in the presence of 5% palladium-on-charcoal catalyst (2.5 g.). The theoretical amount of hydrogen was adsorbed within 90 minutes. The catalyst was removed by filtration (Celite), and the filtrate was treated with concentrated hydrochloric acid (3.75 ml., 45.0 mmoles). The resulting solution was reduced in volume to 100 ml. and diluted with ethyl ether (500 ml.) to deposit a gum. The supernatant liquid was decanted and the remaining gum was triturated repeatedly with ethyl acetate to give a hygroscopic solid, which was collected by filtration and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 3.9 g. (74%); m.p., dec. without melting from 90°; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 223 (19.9), 282 (10.2); *p*H 7–280 (9.9); 0.1 *N* sodium hydroxide, 279 (10.3); methanol, 307 (10.6); $\bar{\nu}$ in cm^{-1}: 3365-3135 (broad, NH); 1645 (broad, NH); 1600, 1580, 1495 (C=C, C=N).

Anal. Calcd. for $C_{13}H_{26}N_6 \cdot 2.5$ HCl: C, 43.67; H, 8.04; Cl, 24.79; N, 23.50. Found: C, 43.68; H, 8.23; Cl, 24.31; N, 23.81.

2,4-Diamino-6-[[4-(diethylamino)-1-methylbutyl]amino]-5-nitropyrimidine Monohydrochloride Three-Fourths Hydrate (**19**).

A mixture of **17** (1.97 g., 10.4 mmoles) and 2-amino-5-diethylaminopentane (1.65 g., 10.4 mmoles) in methanol (75 ml.) was refluxed under nitrogen for 2 hours, then cooled, diluted with ethyl ether (100 ml.), and refrigerated for 18 hours. The light yellow solid that deposited was collected by filtration, washed with ethyl ether, and dried *in vacuo* over phosphorus pentoxide at 78°, yield 2.6 g. (68%); m.p. 183-184°; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 330 (14.2); *p*H 7–270 (4.2), 341 (18.7); 0.1 *N* sodium hydroxide, 269 (4.0), 342 (18.9); $\bar{\nu}$ in cm^{-1}: 3420, 3390, 3300, 3200 (NH).

Anal. Calcd. for $C_{13}H_{25}N_7O_2 \cdot HCl \cdot 3/4\ H_2O$: C, 43.21; H, 7.67; Cl, 9.81; N, 27.13. Found: C, 43.06; H, 7.45; Cl, 9.20; N, 27.01.

3,4,5-Triaminopyridine Dihydrochloride (**22**).

A solution of 3,4-diamino-5-nitropyridine (8) (5.4 g., 35 mmoles) in 95% ethanol (450 ml.) was hydrogenated at room temperature and atmospheric pressure using 5% palladium-on-charcoal (1.0 g.) as catalyst. The theoretical amount of hydrogen was adsorbed within 1 hour. The catalyst was removed by filtration (Celite), and the colorless filtrate was treated with concentrated hydrochloric acid (9.0 ml., 108 mmoles). The white solid that deposited was collected and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 6.0 g. (87%); m.p. 287-289° dec. (oil bath); λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 227 (24.4), 294 (7.7); *p*H 7–234 (29.4), 297 (7.5); $\bar{\nu}$ in cm^{-1}: 3375, 3345, 3290, 3250, 3140, 1675, 1635, 1620 (NH).

Anal. Calcd. for $C_5H_8N_4 \cdot 2HCl$: C, 30.48; H, 5.11; Cl, 35.98; N, 28.43. Found: C, 30.75; H, 5.13; Cl, 35.73; N, 28.44.

8-Amino-2-(*p*-chlorophenyl)pyrido[3,4-*b*]pyrazine (**23**).

To a solution of **22** dihydrochloride (9.85 g., 50.0 mmoles) in water (300 ml.) was added sodium bicarbonate (8.40 g., 100 mmoles), followed by a solution of *p*-chlorophenylglyoxal monohydrate (9.33 g., 50.0 mmoles) in dioxane (75 ml.). The resulting mixture was stirred for 6 hours at room temperature, then 1 hour at reflux. The hot reaction mixture was filtered, and the resulting solid was washed with hot water (3 x 100 ml.) and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 11.8 g. (92%). A 3.0-g. sample of the crude product was recrystallized from boiling methanol (200 ml.), yield 2.7 g.; m.p. 200-202° after drying 1 hour at 100° *in vacuo* over phosphorus pentoxide; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 254 (15.4), 312 (26.4), 420 (5.4); *p*H 7–245 (16.5), 299 (31.4), 345 (sh); 0.1 *N* sodium hydroxide, 246 (16.4), 299 (31.6), 345 (sh); $\bar{\nu}$ in cm^{-1}: 3455, 3280, 3160, 1610 (NH); pmr (10% DMSO-d_6 w/v), δ, 6.35 (2, NH_2), 8.05 (4, C_6H_4), 8.22, 8.63, 9.60 (1, 1, 1, 7-H, 5-H, 3-H).

Anal. Calcd. for $C_{13}H_9ClN_4$: C, 60.83; H, 3.53; N, 21.83. Found: C, 60.65; H, 3.66; N, 21.69.

8-Amino-2-(3,4-dichlorophenyl)pyrido[3,4-*b*]pyrazine (**24**).

To a solution of **22** dihydrochloride (4.34 g., 22 mmoles) in water (50 ml.) was added sodium bicarbonate (1.85 g., 22 mmoles), and the resulting solution was evaporated to dryness and dried azeotropically with ethanol. A solution of 3,4-dichlorophenylglyoxal monohydrate (4.42 g., 20 mmoles) in ethanol (400 ml.) was added to the residue, and the resulting mixture was heated at reflux under nitrogen for 3 hours. The solid that deposited was collected by filtration, washed with water (3 x 50 ml.), and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 6.19 g. The crude product was triturated repeatedly with ethanol, recrystallized from 2:1 methanol-water (900 ml.), and dried at 78° for 4 hours *in vacuo* over phosphorus pentoxide, yield 2.60 g. (45%); m.p. 236-238° dec.; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 257 (14.5), 309 (24.6); $\bar{\nu}$ in cm^{-1}: 3455, 3280, 1630 (NH); pmr (5% trifluoroacetic acid w/v), δ, 7.75 d, 8.28 q, 8.57 d (3, C_6H_3), 8.36 d, 9.11 d, 9.82 (1, 1, 1, 7-H, 5-H, 3-H).

Anal. Calcd. for $C_{13}H_8Cl_2N_4$: C, 53.63; H, 2.77; Cl, 24.36; N, 19.24. Found: C, 53.49; H, 2.97; Cl, 24.36; N, 19.01.

8-Amino-2,3-bis(*o*-tolyl)pyrido[3,4-*b*]pyrazine (**25**).

The free amide of **22** was prepared from the dihydrochloride (2.2 g., 11 mmoles) by the addition of a solution of sodium bicarbonate (1.8 g., 22 mmoles) in water (20 ml.). The solution was evaporated to dryness under reduced pressure, and the resulting residue was dried azeotropically with ethanol. A solution of *o*-tolil (2.4 g., 10 mmoles) in 2-(2-methoxyethoxy)ethanol (50 ml.) was added to the residue, and the mixture was heated at reflux under an air condenser for 48 hours. The cooled mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. The dark brown oily residue was triturated in water (3 x 75 ml.), and the solid that formed was collected and dried *in vacuo* over phosphorus pentoxide, yield 3.1 g. (94%); m.p. 156-160°. The crude product was eluted from a silica gel H column with chloroform and recrystallized from 2:1 ethanol-water, yield 1.6 g. (48%); m.p. 179-181°; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 243 (17.6), 268 (15.6), 317 (11.2); *p*H 7–263 (21.1), 303 (13.3); 0.1 *N* sodium hydroxide, 263 (21.1), 303 (13.4); ethanol, 243 (17.0), 264 (15.7), 309 (15.4); $\bar{\nu}$ in cm^{-1}: 3470, 3385, 1605 (NH).

Anal. Calcd. for $C_{21}H_{18}N_4$: C, 77.28; H, 5.56; N, 17.17. Found: C, 77.15; H, 5.61; N, 17.21.

8-Amino-2,3-bis(*p*-chlorophenyl)pyrido[3,4-*b*]pyrazine (**26**).

A solution of **22** dihydrochloride (2.0 g., 10 mmoles) in water (50 ml.) was treated with sodium bicarbonate (1.6 g., 20 mmoles), and the resulting solution was added to a solution of 4,4'-dichlorobenzil (2.8 g., 10 mmoles) in boiling ethanol (550 ml.). The resulting solution was heated at reflux under nitrogen for 6 hours. The cooled mixture was filtered, and the filtrate was evaporated

to dryness. The residue was triturated in water (3 x 50 ml.), collected by filtration, and dried *in vacuo* over phosphorus pentoxide, yield 3.7 g. (100%). The crude product was eluted from a silica gel H column with chloroform and recrystallized from boiling ethanol. The orange crystalline solid was dried at 78° *in vacuo* over phosphorus pentoxide for 3 hours, yield 2.2 g. (60%); m.p. 180-181°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 244 (18.1), 320 (15.7); *p*H 7–232 (18.5), 319 (15.8); 0.1 *N* sodium hydroxide, 233 (18.6), 318 (16.0); ethanol, 227 (23.8), 315 (22.9); $\bar{\nu}$ in cm^{-1}: 3440, 3340 (broad); 1600 (NH); 1590, 1570, 1550, 1530 (C=C, C=N).

Anal. Calcd. for $C_{19}H_{12}Cl_2N_4$: C, 62.14; H, 3.29; Cl, 19.31; N, 15.26. Found: C, 61.95; H, 3.46; Cl, 19.09; N, 15.06.

8-Amino-2,3-bis(3,4-dichlorophenyl)pyrido[3,4-*b*]pyrazine (**27**).

The free amine of **22** was prepared from the dihydrochloride (1.63 g., 8.25 mmoles) by the addition of a solution of sodium bicarbonate (1.40 g., 16.5 mmoles) in water (25 ml.). The solution was evaporated to dryness under reduced pressure, and the resulting residue was dried azeotropically with ethanol. A solution of crude 3,3′,4,4′-tetrachlorobenzil (5.2 g., 15 mmoles) in butyl alcohol (100 ml.) was added to the residue and the mixture was heated at reflux for 12 hours. The mixture was evaporated to dryness at reduced pressure and the residue was triturated with water (3 x 100 ml.). The red solid that formed was collected and dried *in vacuo* over phosphorus pentoxide, yield 6.2 g. (170%). The crude product was suspended in benzene (50 ml.) and the excess benzil was collected by filtration. The filtrate was then eluted from a silica gel H column with chloroform and recrystallized from 10:1 ethanol-water. The resulting red crystalline product was dried for 5 hours at 78° *in vacuo* over phosphorus pentoxide, yield 3.5 g. (97%); m.p. dec. without melting above 116°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 321 (20.8); *p*H 7–232 (28.2), 325 (22.4); 0.1 *N* sodium hydroxide, 233 (28.8), 327 (22.5); ethanol, 264 (17.5), 315 (29.7); $\bar{\nu}$ in cm^{-1}: 3450, 3380, 1600 (NH); 1595, 1545, 1525 (C=C, C=N).

Anal. Calcd. for $C_{19}H_{10}Cl_4N_4$: C, 52.33; H, 2.31; Cl, 32.51; N, 12.85. Found: C, 52.04; H, 2.49; Cl, 32.72; N, 12.79.

8-Amino-2,3-bis(3,4,5-trimethoxyphenyl)pyrido[3,4-*b*]pyrazine (**28**).

The free amine of **22** was prepared from the dihydrochloride (1.63 g., 8.25 mmoles) by the addition of a solution of sodium bicarbonate (1.39 g., 16.5 mmoles) in water (15 ml.). The solution was evaporated to dryness under reduced pressure and the resulting residue was dried azeotropically with ethanol. A slurry of 3,3′,4,4′,5,5′-hexamethoxybenzil (2.93 g., 7.50 mmoles) in butyl alcohol (75 ml.) was added to the residue, and the mixture was heated at reflux under nitrogen for 9 hours. The butyl alcohol was removed by evaporation under reduced pressure, and the yellow residue was triturated in water (2 x 100 ml.), collected by filtration, and dried *in vacuo* over phosphorus pentoxide, yield 3.55 g. (98%). Recrystallization of this solid from boiling ethanol (300 ml.) gave the analytically pure product, yield 3.20 g. (89%); m.p. 217-219°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 267 (19.4), 326 (15.7); *p*H 7–265 (23.3), 316 (16.9); 0.1 *N* sodium hydroxide, 265 (23.3), 316 (16.8); ethanol, 266 (20.2), 328 (19.2); $\bar{\nu}$ in cm^{-1}: 3470, 3375, 1610 (NH).

Anal. Calcd. for $C_{25}H_{26}N_4O_6$: C, 62.75; H, 5.48; N, 11.71. Found: C, 62.55; H, 5.74; N, 11.64.

2-(*o*-Chlorophenyl)-5-[[4-(diethylamino)-1-methylbutyl]amino]-pyrido[3,4-*b*]pyrazine (**29**).

A solution of 36 (5.95 g., 20.2 mmoles) in ethanol (200 ml.) was hydrogenated over Raney nickel (~15 g.) at an initial hydrogen pressure of 3.5 kg.-cm^{-2}. The catalyst was removed under nitrogen, and the colorless filtrate was treated with a solution of *o*-chlorophenylglyoxal monohydrate (4.10 g., 22.0 mmoles) in ethanol (50 ml.). The resulting red solution was stirred at room temperature for 20 hours, refluxed under nitrogen for 1 hour, and evaporated to dryness *in vacuo*. The residual brown oil was slurried in water (300 ml.), and extracted into chloroform (3 x 200 ml.). The combined extracts were washed with a saturated solution of sodium bisulfite, then with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*, yield 7.4 g. (92%). A 6.5-g. sample of this brown gum was dissolved in chloroform and poured onto a silica gel H column (300 g.). Elution with chloroform-methanol (9:1) gave a total recovery of 5.3 g. (81%), of which 4.7 g. was chromatographically homogeneous. An aqueous slurry of this homogeneous material was treated with excess 50% sodium hydroxide and extracted with chloroform (3 x 150 ml.). The combined extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The residual amber oil was dried by prolonged evacuation on the oil pump, yield 4.6 g. (57%); λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 284 (12.4), 368 (10.4); *p*H 7–231 (21.4), 283 (16.7); 0.1 *N* sodium hydroxide, 232 (20.7), 284 (16.0); $\bar{\nu}$ in cm^{-1}: 3400 (NH); 1580, 1520 (C=C, C=N); pmr (12.5% deuteriochloroform w/v), δ, 7.57 m (4, C_6H_4), 7.07 d, 8.21 d, 8.93 (1, 1, 1, 8-H, 7-H, 3-H).

Anal. Calcd. for $C_{22}H_{28}ClN_5$: C, 66.40; H, 7.09; Cl, 8.91; N, 17.60. Found: C, 66.26; H, 7.05; Cl, 9.17; N, 17.53.

8-Bromo-2-(*o*-chlorophenyl)-5-[[4-(diethylamino)-1-methylbutyl]-amino]pyrido[3,4-*b*]pyrazine Monohydrochloride (**30**).

Liquid bromine (0.78 g., 4.9 mmoles) was added dropwise to a solution of **29** (1.80 g., 4.53 mmoles) in glacial acetic acid (20 ml.), and the resulting orange solution was stirred for 18 hours. The reaction mixture was evaporated to dryness *in vacuo*, and a solution of the residue in water (100 ml.) was adjusted to *p*H 10 with 50% sodium hydroxide and extracted with chloroform (2 x 100 ml.). The combined extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was dissolved in dry ethanol (50 ml.), and the solution was acidified with 3 *N* ethanolic hydrochloric acid (3 ml.), treated with charcoal, and filtered through Celite. The filtrate was diluted with ethyl ether (300 ml.) to deposit a yellow oil that solidified after vigorous magnetic stirring. This solid material was precipitated twice from ethanol-ethyl ether to give a bright yellow, chromatographically homogeneous powder, which was dried *in vacuo* over phosphorus pentoxide at 100°, yield 1.01 g. (43%); m.p. 223-225° dec.; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 227 (19.2), 293 (12.2), 377 (8.8); *p*H 7–234 (20.5), 291 (14.5); 0.1 *N* sodium hydroxide, 239 (21.5), 299 (16.7); $\bar{\nu}$ in cm^{-1}: 3435, 3350 (NH); 1590, 1540 (C=C, C=N); pmr (15% DMSO-d_6 w/v), δ, 7.74 m (4, C_6H_4), 8.23, 9.30 (1, 1, 7-H, 3-H).

Anal. Calcd. for $C_{22}H_{27}BrClN_5 \cdot HCl$: C, 51.48; H, 5.50; Br, 15.57; N, 13.64. Found: C, 50.86; H, 5.55; Br, 16.03; N, 13.78.

2-(*p*-Chlorophenyl)-5-[[4-(diethylamino)-1-methylbutyl]amino]-pyrido[3,4-*b*]pyrazine (**31**).

A solution of **36** (5.95 g., 20.2 mmoles) in ethanol (200 ml.) was hydrogenated over Raney nickel (~15 g.) at an initial hydrogen pressure of 3.5 kg.-cm^{-2}. The catalyst was filtered off under nitrogen, and the colorless filtrate was treated with solid *p*-chlorophenylglyoxal monohydrate (4.10 g., 22.0 mmoles). The resulting red solution was stirred at room temperature for 20 hours, refluxed

under nitrogen for 1 hour, then evaporated to dryness. The residual brown oil was slurried in water (300 ml.) and extracted into chloroform (3 x 200 ml.). The combined extracts were washed with a saturated solution of sodium bisulfite, then with water, and dried over sodium sulfate. The chloroform solution was evaporated to dryness *in vacuo* to give a viscous amber gum, yield 6.8 g. (85%). The brown gum (6.2 g.) was dissolved in chloroform-methanol (9:1) and poured onto a silica gel H column (300 g.). Elution with chloroform-methanol (4:1) gave 5.2 g. (84% recovery) of amber oil, which was collected in seven fractions. The last two fractions (3.5 g.) were homogeneous, and an aqueous slurry of this oil was treated with excess 50% sodium hydroxide solution. The resulting mixture was extracted with chloroform, and the extract was washed with water, dried over sodium sulfate, and evaporated to dryness. The amber oil was dried by prolonged evacuation on the oil pump, yield 2.3 g. (29%); λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 262 (14.7), 296 (17.0), 372 (14.6); *p*H 7–237 (25.5), 300 (25.1); $\bar{\nu}$ in cm^{-1}: 3400 (NH); 1580, 1520 (C=C, C=N); pmr (12.5% deuteriochloroform w/v), δ, 7.80 m (4, C_6H_4), 7.03 d, 8.18 d, 8.97 (1, 1, 1, 8-H, 7-H, 3-H).

Anal. Calcd. for $C_{22}H_{28}ClN_5$: C, 66.40; H, 7.09; Cl, 8.91; N, 17.60. Found: C, 66.30; H, 7.15; Cl, 9.06; N, 17.69.

5-[[4-(Diethylamino)-1-methylbutyl]amino]pyrido[3,4-*b*]pyrazin-2(1*H*)-one (**32**).

A solution of **36** (10.5 g., 35.6 mmoles) in 1-propanol (200 ml.) was hydrogenated over Raney nickel catalyst (~15 g.) at an initial hydrogen pressure of 3.5 kg.-cm^{-2}. The catalyst was filtered off under nitrogen, and the colorless filtrate was treated with freshly distilled ethyl glyoxylate (5.40 g., 52.9 mmoles). The orange solution was stirred at room temperature for 72 hours, refluxed under nitrogen for 4 hours, then cooled and evaporated to dryness *in vacuo*. The residual red gum was dissolved in chloroform and poured onto a silica gel H column (300 g.). Elution with chloroform-methanol (4:1) gave a diffuse product band that was collected in eleven fractions, each of which was evaporated to dryness *in vacuo*. The first group of these solids were shown by thin-layer chromatography to contain a trace contaminant. These solids were combined and dissolved in ethanol (100 ml.); the solution was charcoaled, filtered, acidified with excess 1 *N* ethanolic hydrochloric acid, and diluted with ethyl ether (600 ml.) to deposit the hydrochloride salt of the product, yield 6.5 g. (48%). The second group of chromatographically homogeneous solids were combined and recrystallized by extraction into ethyl ether (300 ml.) in a Soxhlet apparatus. After cooling the extract, the deposit of yellow powder was collected by filtration and dried *in vacuo* over phosphorus pentoxide at 78°, yield 2.4 g. (23%); m.p. 118-120° dec.; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 238 (27.2), 285 (9.4), 300 (sh), 371 (1.7); *p*H 7–243 (9.5), 278 (14.7), 387 (5.5); 0.1 *N* sodium hydroxide, 244 (10.4), 279 (15.4); $\bar{\nu}$ in cm^{-1}: 3400 (NH); 1660 (C=O); 1600, 1545, 1500 (C=C, C=N); pmr (10% DMSO-d_6 w/v), δ, 6.80 d, 7.75 d, 8.31 (1, 1, 1, 8-H, 7-H, 3-H).

Anal. Calcd. for $C_{16}H_{25}N_5O$: C, 63.34; H, 8.31; N, 23.08. Found: C, 63.39; H, 8.43; N, 23.07.

The total yield of free amine and its hydrochloride was 71%.

2-Chloro-5-[[4-(diethylamino)-1-methylbutyl]amino]pyrido[3,4-*b*]-pyrazine (**33**).

A suspension of **32** (6.40 g., 21.1 mmoles) in phosphorus oxychloride (350 ml.) was refluxed under nitrogen for 5 hours. The resulting clear, dark solution was evaporated *in vacuo*, and the residual gum was dissolved in water (~500 ml.). This dark solution was treated with charcoal, adjusted to *p*H 11 with 50% sodium hydroxide, and extracted with chloroform (3 x 200 ml.). The extract was washed with water, dried over sodium sulfate, and evaporated to a dark oil *in vacuo*. An ethanol solution (300 ml.) of this oil (4.7 g.) was treated with charcoal, filtered, and evaporated to dryness. The residue was dissolved in ethyl ether (150 ml.) and filtered to remove tiny specks of dark resinous material. Evaporation of the ethyl ether and prolonged drying of the residue over phosphorus pentoxide under high vacuum gave a clear amber oil, yield 3.9 g. (57%); λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 262 (12.4), 300 (5.8), 369 (6.5); *p*H 7–272 (18.5), 320 (3.1), 335 (sh); 0.1 *N* sodium hydroxide, 272 (17.7), 321 (3.0), 335 (sh); $\bar{\nu}$ in cm^{-1}: 3410 (NH); 1575, 1535, 1520 (C=C, C=N); pmr (15% deuteriochloroform w/v), δ, 6.99 d, 8.19 d, 8.79 (1, 1, 1, 8-H, 7-H, 3-H).

Anal. Calcd. for $C_{16}H_{24}ClN_5$: C, 59.71; H, 7.52; Cl, 11.0; N, 21.76. Found: C, 59.69; H, 7.54; Cl, 10.8; N, 21.92.

8-Bromo-2-chloro-5-[[4-(diethylamino)-1-methylbutyl]amino]-pyrido[3,4-*b*]pyrazine Monohydrochloride (**34**).

Liquid bromine (0.59 g., 3.7 mmoles) was added to a solution of **33** (1.20 g., 3.7 mmoles) in glacial acetic acid (10 ml.). After standing for 2 hours, the reaction mixture was evaporated to dryness *in vacuo*. The resulting residue was twice triturated with ether (25 ml.) and evaporated to dryness to give a crusty yellow solid, which was ground in a mortar under ethyl acetate and dried over phosphorus pentoxide *in vacuo*;s yield 1.2 g. The solid was dissolved in water (75 ml.); 50% sodium hydroxide (0.3 ml.) was added, and the resulting mixture was extracted with chloroform (2 x 100 ml.). The combined extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The residual oil was dissolved in absolute ethanol (50 ml.), and the solution was acidified with excess 1 *N* ethanolic hydrochloric acid and diluted with ethyl ether (500 ml.). After standing in the refrigerator for 48 hours, the orange precipitate was collected by filtration and dried *in vacuo* over phosphorus pentoxide at 78°, yield 1.2 g. (74%); m.p. sinters and chars ~223°, decomposes 233°; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 273 (12.0), 312 (4.8), 379 (5.9); *p*H 7–240 (13.7), 278 (16.5), 343 (2.8); 0.1 *N* sodium hydroxide, 241 (13.9), 278 (16.1), 345 (2.8); $\bar{\nu}$ in cm^{-1}: 3400 (NH); 1570, 1535, 1510 (C=C, C=N); pmr (15% DMSO-d_6 w/v), δ, 8.33, 9.15 (1, 1, 7-H, 3-H).

Anal. Calcd. for $C_{16}H_{23}BrClN_5 \cdot HCl$: C, 43.95; H, 5.53; Br, 18.28; Cl, 16.22; N, 16.02. Found: C, 44.24; H, 5.73; Br, 18.07; Cl, 16.04; N, 15.96.

4-Amino-2-[[4-(diethylamino)-1-methylbutyl]amino]-3-nitropyridine (**36**).

A solution of **35** (2.00 g., 11.5 mmoles) and 2-amino-5-diethylaminopentane (1.84 g., 11.6 mmoles) in butyl alcohol (35 ml.) was refluxed under nitrogen for 18 hours. The reaction mixture was poured into water (500 ml.) containing 10 *M* sodium hydroxide (1.5 ml.), and the resulting mixture was extracted with chloroform (3 x 150 ml.). The combined extracts was dried over sodium sulfate and evaporated *in vacuo* to give a mobile red oil. The oil was redissolved in chloroform (~20 ml.) and poured onto a silica gel H column (100 g.) which had been prewashed with chloroform. Elution with chloroform gave three visibly distinct zones. The silica gel was extruded, and the fastest moving zone was extracted with hot methanol and filtered. Evaporation of the filtrate followed by prolonged evacuation on the oil pump gave an amber oil, yield 2.50 g. (74%); λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid, 236 (20.1), 339 (9.1); *p*H 7–255 (sh), 348 (8.2); 0.1 *N* sodium hydroxide, 255 (sh), 349 (8.1); $\bar{\nu}$ in cm^{-1}: 3460,

3425, 3350, 1600 (NH); 1585, 1510 (C=C, C=N); 1545, 1320 (NO_2).

Anal. Calcd. for $C_{14}H_{25}N_5O_2$: C, 56.93; H, 8.53; N, 23.71. Found: C, 56.90; H, 8.64; N, 23.59.

3,4-Diamino-2-[[4-(diethylamino)-1-methylbutyl]amino]pyridine Trihydrochloride (**37**).

A solution of **36** (3.00 g., 10.2 mmoles) in ethanol (100 ml.) was hydrogenated over Raney nickel catalyst at an initial pressure of 3.5 kg.-cm^{-2}. The catalyst was filtered off under nitrogen, and the colorless filtrate was acidified with 1.26 *N* ethanolic hydrochloric acid (28 ml.) and evaporated *in vacuo* on a lukewarm water bath. Under high vacuum the resulting viscous residue crystallized to a brittle white solid, which was collected under nitrogen and dried over phosphorus pentoxide *in vacuo* at room temperature; yield 3.40 g. (89%); m.p. indefinite, softens gradually above ~105°; λ max in nm ($\epsilon \times 10^{-3}$): 0.1 *N* hydrochloric acid, 288 (7.7); *p*H 7–296 (9.6); 0.1 *N* sodium hydroxide, 289 (5.2); $\bar{\nu}$ in cm^{-1}: 3280, 3135 (broad); 1655 (NH); 1605, 1485 (C=C, C=N).

Anal. Calcd. for $C_{14}H_{27}N_5 \cdot 3HCl$: C, 44.87; H, 8.07; Cl, 28.38; N, 18.68. Found: C, 45.05; H, 8.22; Cl, 28.15; N, 18.48.

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