Synthesis of Potential Antimalarial Agents. VIII. Azaquinolines. II. Preparation of Some 1,5-Naphthyridines and Pyrido[3,2-*d*]pyrimidines (1).

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The antimalarial activity against *Plasmodium berghei* of some derivatives of the pyrido[2,3-*b*]pyrazine ring system (2) prompted us to prepare some related compounds in the 1,5-naphthyridine and pyrido[3,2-*d*]pyrimidine ring systems.

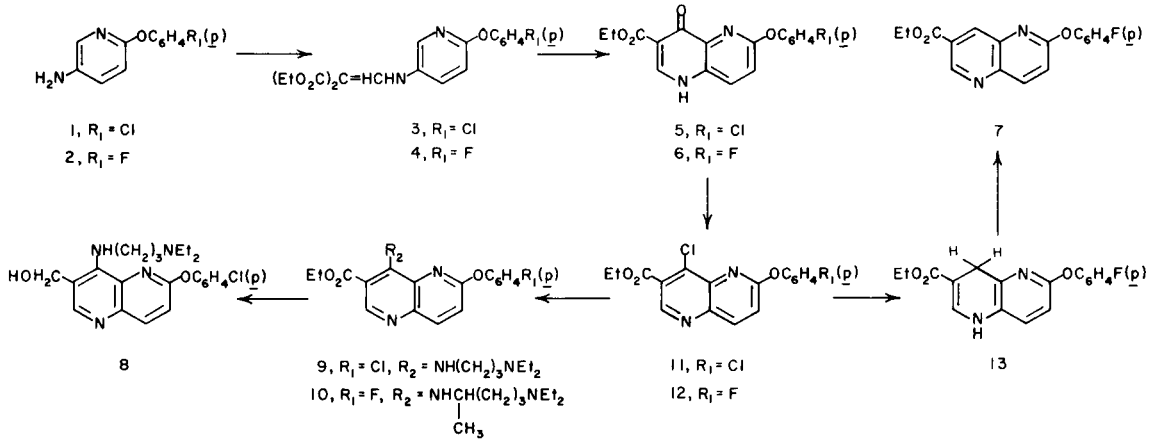
Reaction of 2-chloro-5-nitropyridine with *p*-chlorophenol in ethanolic potassium hydroxide gave 2-(*p*-chlorophenoxy)-5-nitropyridine, which was reduced with stannous chloride to give the 5-aminopyridine **1** (3). Treatment of the latter with diethyl ethoxymethylenemalonate and cyclization of the resulting intermediate **3** in hot diphenyl ether gave the 4-oxo(1*H*)-1,5-naphthyridine **5**. The chlorodehydroxylation of **5** with phosphorus oxychloride gave the 4-chloro-1,5-naphthyridine **11**. Reaction of **11** with 3-(diethylamino)propylamine replaced the chloro group to give **9**. The ester group of the latter was reduced with lithium aluminum hydride to give the 1,5-naphthyridinemethanol **8**. Methods similar to those described above were used for the preparation of the 6-(*p*-fluorophenoxy)naphthyridine **12** *via* **2**, **4**, and **6**. Reaction of **12** with 2-amino-5-(diethylamino)pentane gave **10**, and dehydrohalogenation of **12** with a palladium-on-charcoal catalyst gave the dihydronaphthyridine **13**. The structural assignment of the latter is based on the pmr spectrum of the product in DMSO-d_6, which showed the ring CH_2 as a singlet and the NH as a doublet. Oxidation of **13** with potassium permanganate gave **7**.

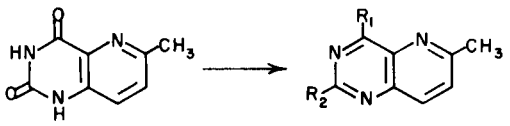
To prepare the pyrido[3,2-*d*]pyrimidine compounds, 5-aminouracil was treated with crotonaldehyde to give **14** (4). The chlorodehydroxylation of **14** with phosphorus oxychloride gave the dichloro compound **15**. Reaction of the latter with ammonia, 3-diethylaminopropylamine and 2-amino-5-diethylaminopentane, respectively, gave **16**, **17**, and **18**. Under vigorous conditions the reaction of **15** with 2-amino-5-diethylaminopentane replaced both chloro groups to give **19**.

All compounds except **8** (6) were tested against lethal, blood-induced *Plasmodium berghei* infections in mice (5). The naphthyridines were non-toxic but less active than related compounds in the pyrido[2,3-*b*]pyrazine series (2). The most active, **10**, gave an increase in mean survival time of 6.1 days at the 640 mg./kg. dose. The pyrido[3,2-*d*]pyrimidines **14-19** were toxic at the 640 mg./kg. dose, but showed no significant activity at lower doses.

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.





14

15, $R_1 = R_2 = Cl$
16, $R_1 = NH_2$, $R_2 = Cl$
17, $R_1 = NH(CH_2)_3NEt_3$, $R_2 = Cl$
18, $R_1 = NHCH(CH_2)_3NEt_2$ (CH$_3$), $R_2 = Cl$
19, $R_1 = R_2 = NHCH(CH_2)_3NEt_2$ (CH$_3$)

2-(*p*-Chlorophenoxy)-5-nitropyridine (3).

To a warmed solution of potassium hydroxide (5.60 g., 100 mmoles) and *p*-chlorophenol (12.9 g., 100 mmoles) in ethanol (150 ml.) was added 2-chloro-5-nitropyridine (15.9 g., 100 mmoles), and the resulting mixture was heated at reflux for 2 hours. The residue obtained upon evaporation of the solvent was washed with water (4 x 175 ml.) and recrystallized from boiling ethanol (150 ml.), yield 18.2 g. (73%); m.p. 93-95°; λ max in nm (ϵ x 10^{-3}): *p*H 7–296 (11.2); $\bar{\nu}$ in cm^{-1}: 1600, 1585, 1570, 1510 (C=C, C=N); 1350 ($-NO_2$).

Anal. Calcd. for $C_{11}H_7ClN_2O_3$: C, 52.72; H, 2.82; N, 11.18. Found: C, 52.85; H, 2.99: N, 11.39.

2-(*p*-Fluorophenoxy)-5-nitropyridine.

This compound was prepared by a similar process from 2-chloro-5-nitropyridine (31.7 g., 200 mmoles) and *p*-fluorophenol (22.4 g., 200 mmoles), yield 35.6 g. (75%); m.p. 95-97°.

Anal. Calcd. for $C_{11}H_7FN_2O_3$: C, 56.42; H, 3.01; N, 11.96. Found: C, 56.28; H, 3.15; N, 11.87.

5-Amino-2-(*p*-chlorophenoxy)pyridine Monohydrochloride (**1**) (3).

A solution of 2-(*p*-chlorophenoxy)-5-nitropyridine (10.8 g., 43.0 mmoles) and stannous chloride dihydrate (76.7 g., 300 mmoles) in 35% hydrochloric acid (100 ml.) was stirred and heated at 100° for 3 hours. The cooled mixture was evaporated to dryness at reduced pressure, and the residue was made alkaline with 20% sodium hydroxide (500 ml.). The insoluble solids were removed by filtration (Celite) and washed with ethyl ether. The combined filtrate and wash was extracted with ethyl ether (5 x 100 ml.) and evaporated to dryness. The residue (10.1 g.) was dissolved in ethanol (100 ml.) and treated with concentrated hydrochloric acid (4.1 ml., 50 mmoles). The solid that deposited was collected by filtration and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 8.8 g. (80%), m.p. dec. without melting from 226°; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid 269 (4.5); *p*H 7–238 (17.1), 304 (3.4); 0.1 *N* sodium hydroxide 238 (17.1), 304 (3.4); $\bar{\nu}$ in cm^{-1}: 3430 broad (NH); 1615 (NH); 1595, 1565, 1510 (C=C, C=N).

Anal. Calcd. for $C_{11}H_9ClN_2O{\cdot}HCl$: C, 51.38; H, 3.92; N, 10.89. Found: C, 51.31; H, 3.91; N, 11.10.

5-Amino-2-(*p*-fluorophenoxy)pyridine Monohydrochloride (**2**).

This compound was prepared by a similar reduction from 2-(*p*-fluorophenoxy)-5-nitropyridine (3.51 g., 15.0 mmoles) and stannous chloride (23 g., 90 mmoles) in concentrated hydrochloric acid (35 ml.), yield 2.78 g., (77%). This sample underwent decomposition from 220°.

Anal. Calcd. for $C_{11}H_9FN_2O{\cdot}HCl$: C, 54.90; H, 4.19; N, 11.64. Found: C, 54.67; H, 4.07; N, 11.53.

Ethyl 6-(*p*-Chlorophenoxy)-1,4-dihydro-4-oxo-1,5-naphthyridine-3-carboxylate (**5**).

A solution of sodium methoxide (1.42 g., 26.3 mmoles) in methanol (15 ml.) was added to **1** monohydrochloride (6.75 g., 26.3 mmoles). Diethyl ethoxymethylenemalonate (5.69 g., 26.3 mmoles) was then added, and the resulting mixture was heated with stirring in a hot water bath for 1 hour. The crude **3** (12.1 g.) was collected by filtration and added to vigorously boiling phenyl ether (40 ml.) over a 10-minute period. The resulting solution was boiled an additional 15 minutes, cooled to room temperature, and diluted with petroleum ether (b.p. 60-68°) (60 ml.). The solid that formed was collected by filtration, washed with acetone (2 x 25 ml.), then with water (4 x 25 ml.), and dried *in vacuo* at room temperature over phosphorus pentoxide, yield 5.8 g. (64%); m.p. 274-276° dec.; λ max in nm (ϵ x 10^{-3}): *p*H 7–262 (26.4), 323 (sh), 337 (sh); $\bar{\nu}$ in cm^{-1}: 1710, 1690 (C=O); 1610 (NH); 1590, 1580, 1555, 1525, 1510 (C=C, C=N); pmr (10% trifluoroacetic acid w/v), δ, 1.57 t (3, CH_3), 4.75 q (2, CH_2), 7.40 q (4, C_6H_4), 7.82 d (1, 8-H), 8.75 d (1, 7-H), 9.42 (1,2-H).

Anal. Calcd. for $C_{17}H_{13}ClN_2O_4$: C, 59.23; H, 3.80; N, 8.12. Found: C, 59.06; H, 3.85; N, 8.00.

Ethyl 6-(*p*-Fluorophenoxy)-1,4-dihydro-4-oxo-1,5-naphthyridine-3-carboxylate (**6**).

This compound was prepared in a similar manner *via* **4** from **2** (20.4 g., 100 mmoles) and diethyl ethoxymethylenemalonate (21.6 g., 100 mmoles), yield 23.5 g. (71%). A portion of this sample (3.3 g.) was dissolved in dimethyl sulfoxide (70 ml.), treated with charcoal, reprecipitated with water (700 ml.), and then recrystallized from dioxane (400 ml.): yield 1.0 g.; m.p. 273-276° dec. Thin-layer chromatogram (Brinkmann silica gel H), R_f 0.44 (86:14 butanol-water).

Anal. Calcd. for $C_{17}H_{13}FN_2O_4{\cdot}3/4\ H_2O$: C, 59.74; H, 4.28; N, 8.20. Found; C, 60.04; H, 4.04; N, 8.16.

A portion of this sample was dried *in vacuo* over phosphorus pentoxide at 100°.

Anal. Calcd. for $C_{17}H_{13}FN_2O_2{\cdot}1/2\ H_2O$: C, 60.53; H, 4.18; N, 8.30. Found: C, 60.28; H, 3.76; N, 8.37.

Ethyl 6-(*p*-Fluorophenoxy)-1,5-naphthyridine-3-carboxylate (**7**).

A solution of **13** (628 mg., 3.00 mmoles) in acetone (60 ml.) was treated dropwise with a solution of potassium permanganate (210 mg., 1.30 mmoles) in acetone (60 ml.). The manganese dioxide was removed by filtration and washed with acetone. The residue obtained from the combined filtrate and washings was purified by sublimation at 115°/1 mm: yield 604 mg. (97%); m.p. 116-118°; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid 222 (12.2), 325 (8.7), 335 (9.5); *p*H 7–222 (16.7), 322 (8.1), 333 (8.2); 0.1 *N* sodium hydroxide 318 (9.2), 330 (9.5); $\bar{\nu}$ in cm^{-1}: 1715 (C=O); 1610, 1600, 1505 (C=C, C=N); pmr (10% DMSO-d_6 w/v), δ, 7.61 d (J_{78} 9hz, 1, 8-H), 8.34 d (J_{24} 2hz, 1, 4-H), 8.47 d (1, 7-H), 9.19 d (1, 2-H).

Anal. Calcd. for $C_{17}H_{13}FN_2O_3$: C, 65.38; H, 4.20; N, 8.97. Found: C, 65.43; H, 4.34; N, 8.75.

6-(*p*-Chlorophenoxy)-4-[[3-(diethylamino)propyl]amino]-1,5-naphthyridine-3-methanol Dihydrochloride (**8**).

A mixture of lithium aluminum hydride (0.30 g., 8.0 mmoles) in ethyl ether (10 ml.) was stirred for 10 minutes, and a solution of **9** (2.1 g., 4.6 mmoles) in ethyl ether (50 ml.) was added slowly.

The resulting mixture was stirred at room temperature for 1 hour, and ethyl acetate (1.0 ml.) was added to destroy the excess lithium aluminum hydride. The mixture was poured into 1 *N* sulfuric acid (50 ml.) and extracted with ethyl ether (3 x 50 ml.). The aqueous layer was made basic with 50% sodium hydroxide and again extracted with ethyl ether (3 x 100 ml.). The combined extracts were washed with water (2 x 25 ml.), evaporated to dryness, and the resulting residue was dried azeotropically with benzene; yield 1.8 g. of a yellow oil. This oil was treated with 1 *N* hydrochloric acid (4.4 ml.), and the resulting mixture was filtered. The filtrate was evaporated to dryness and dried azeotropically with ethanol. The residue was triturated in acetonitrile, and the solid that formed was collected by filtration and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 0.78 g. (32%). The crude product was recrystallized from 2-propanol (65 ml.), yield 0.29 g. (12%), m.p. 220° dec.; λ max in nm (ϵ x 10^{-3}): *p*H 7–260 (26.7); 0.1 *N* sodium hydroxide 263 (26.0); $\bar{\nu}$ in cm^{-1}: 3230 (NH); 1630, 1615 (NH); 1595, 1575, 1535 (C=C, C=N); pmr (10% trifluoroacetic acid w/v), δ, 5.05 (CH_2OH), 7.40 q (C_6H_4), 7.63 d (8-H), 8.27 (2-H), 8.33 d (7-H).

Anal. Calcd. for $C_{22}H_{27}ClN_4O_2 \cdot 2HCl$: C, 54.16; H, 5.99; Cl, 21.80; N, 11.48. Found: C, 54.21; H, 6.10; Cl, 21.41; N, 11.26.

Ethyl 4-[[3-(Diethylamino)propyl]amino]-6-(*p*-chlorophenoxy)-1,5-naphthyridine-3-carboxylate (**9**).

A solution of **11** (3.5 g., 15 mmoles) and 3-diethylaminopropylamine (3.9 g., 30 mmoles) in ethanol (250 ml.) was heated at reflux for 6 hours and evaporated to dryness *in vacuo*. The residue was triturated in water (3 x 100 ml.), and the solid that formed was collected by filtration and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 6.53 g. (95%). The crude product was recrystallized from petroleum ether (b.p. 96-100°) (300 ml.), yield 4.1 g. (60%), m.p. 95-96°; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid 222 (24.3), 264 (21.9), 272 (24.3), 310 (sh), 338 (sh), 356 (sh); *p*H 7–276 (2.77), 354 (sh), 371 (sh); $\bar{\nu}$ in cm^{-1}: 3285, 3245, 3175 (NH); 1685 (C=O); 1670 (NH); 1605, 1590, 1580, 1530 (C=C, C=N); 830 (*p*-substituted phenyl); pmr (<5% DMSO-d_6 w/v), δ, 7.38 q (C_6H_4), 7.47 d (8-H), 8.20 d (1, 7-H), 8.80 (1, 2-H).

Anal. Calcd. for $C_{24}H_{29}ClN_4O_3$: C, 63.08; H, 6.40; N, 12.26. Found: C, 63.30; H, 6.45; N, 12.15.

Ethyl 4-[[4-(Diethylamino)-1-methylbutyl]amino-6-(*p*-fluorophenoxy)-1,5-naphthyridine-3-carboxylate Monohydrochloride Hemihydrate (**10**).

A solution of **12** (5.2 g., 16 mmoles) and 2-amino-5-diethylaminopentane (4.8 g., 30 mmoles) in ethanol (250 ml.) was heated at reflux for 6 hours and evaporated to dryness *in vacuo*. The residue was suspended in water (500 ml.), extracted with benzene (3 x 100 ml.), and the combined extracts were evaporated to dryness *in vacuo*, yield 6.15 g. (88%). This residue was dissolved in ethanol (250 ml.) (charcoal), filtered, and acidified with concentrated hydrochloric acid (1.1 ml.). The resulting solution was evaporated to dryness, dried azeotropically with ethanol, and triturated in acetonitrile (50 ml.). The solid that formed was collected by filtration and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 3.0 g. (39%), m.p. 146-148° dec.; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid 227 (sh), 265 (20.6), 273 (22.4), 312 (7.7), 325 (7.1), 342 (8.0), 357 (7.2); *p*H 7–230 (sh), 277 (25.9), 357 (5.6), 373 (4.7); $\bar{\nu}$ in cm^{-1}: 3380, 3340, 3170 (NH); 1675 (C=O); 1615 (NH); 1595, 1575, 1530, 1505 (C=C, C=N); 840 (*p*-substituted phenyl).

Anal. Calcd. for $C_{26}H_{33}FN_4O_3 \cdot HCl \cdot 1/2\ H_2O$: C, 60.75; H, 6.86; N, 10.90. Found: C, 60.64; H, 7.19; N, 11.19.

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

Anal. Calcd. for $C_{26}H_{33}FN_4O_3 \cdot HCl$: C, 7.02; N, 11.09. Found: Cl, 7.00; N, 11.03.

An additional 2.9 g. (38%), m.p. 130-135° dec., of the product was obtained by trituration in ethyl ether of the residue from the acetonitrile filtrate.

Ethyl 4-Chloro-6-(*p*-chlorophenoxy)-1,5-naphthyridine-3-carboxylate (**11**).

A mixture of **5** (3.45 g., 10.0 mmoles) in phosphorus oxychloride (25 ml.) was heated at reflux for 1 hour. The resulting solution was concentrated to a small volume at reduced pressure and carefully added with vigorous stirring to ice (200 g.). The off-white solid that formed was collected by filtration and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 3.5 g. (96%). The crude product (3.4 g.) was recrystallized from ethanol (225 ml.) (charcoal), yield 2.1 g., m.p. 92-93°; λ max in nm (ϵ x 10^{-3}): 0.1 *N* sodium hydroxide 220 (41.0), 320 (10.5), 330 (11.0); $\bar{\nu}$ in cm^{-1}: 1705 (C=O); 1610, 1585, 1580, 1570, 1540 (C=C, C=N); 820 (*p*-substituted phenyl).

Anal. Calcd. for $C_{17}H_{12}Cl_2N_2O_3$: C, 56.22; H, 3.33; N, 7.71. Found: C, 56.16; H, 3.50; N, 7.67.

Ethyl 4-Chloro-6-(*p*-fluorophenoxy)-1,5-naphthyridine-3-carboxylate (**12**).

This compound was prepared by a similar process from **6** (13.1 g., 40.0 mmoles) and phosphorus oxychloride (100 ml.); yield 13.1 g. (95%). A portion of this sample (2.1 g.) was extracted with hot petroleum ether (b.p. 96-100°) (2 x 250 ml.). Evaporation of the extract *in vacuo* gave the analytical sample, yield 1.8 g., m.p. 87-89°; λ max in nm (ϵ x 10^{-3}): *p*H 7–224 (38.8), 328 (8.3); $\bar{\nu}$ in cm^{-1}: 1705 (C=O); 1615, 1575, 1545, 1505 (C=C, C=N); 830 (*p*-substituted phenyl).

Anal. Calcd. for $C_{17}H_{12}ClFN_2O_3$: C, 58.89; H, 3.49; N, 8.08. Found: C, 59.00; H, 3.70; N, 8.10.

Ethyl 6-(*p*-Fluorophenoxy)-1,4-dihydro-1,5-naphthyridine-3-carboxylate (**13**).

A solution of **12** (1.73 g., 5.00 mmoles) in dioxane (50 ml.) containing triethylamine (1.38 ml., 10.0 mmoles) was hydrogenated at atmospheric pressure and room temperature in the presence of 5% palladium-on-charcoal catalyst (1.0 g.). The catalyst was removed by filtration (Celite) and washed with dioxane (3 x 25 ml.). The residue was obtained by evaporation of the combined filtrate and washings was extracted with ethanol (25 ml.), then recrystallized from benzene, yield 0.80 g. (51%), m.p. 188-190°; λ max in nm (ϵ x 10^{-3}): 0.1 *N* hydrochloric acid 262 (6.6), 337 (16.0); $\bar{\nu}$ in cm^{-1}: 3235 (NH); 1705, 1670, 1650 (C=O, NH); 1600, 1585, 1520, 1500 (C=C, C=N); pmr (10% DMSO-d_6 w/v), δ, 1.20 t (3, CH_3), 3.53 (2 ring CH_2), 4.07 q (2, CH_2), 6.96 m (C_6H_4, 2-H, 7-H, 8-H), 8.90 d (1, NH).

Anal. Calcd. for $C_{17}H_{15}FN_2O_3$: C, 64.96; H, 4.81; N, 8.91. Found: C, 64.99; H, 5.01; N, 8.87.

2,4-Dichloro-6-methylpyrido[3,2-*d*]pyrimidine (**15**).

A mixture of **14** (4) (20.0 g., 113 mmoles) in freshly distilled phosphorus oxychloride (500 ml.) was heated at reflux with stirring for 24 hours. The excess phosphorus oxychloride was removed by evaporation at reduced pressure, and the semisolid residue was added to ice (1000 g.) with vigorous stirring. The

resulting mixture was extracted with chloroform (3 x 500 ml.), and the chloroform extracts were combined and evaporated to dryness; yield 17.0 g. The product was purified by recrystallization from petroleum ether (b.p. 85-105°, 1500 ml.), yield 11.5 g. (48%), m.p. 150-152°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid 252 (sh), 315 (6.3); *p*H 7–252 (sh), 315 (6.3); ethanol 309 (5.9), 321 (5.9); $\bar{\nu}$ in cm^{-1}: 3065, 3055, 3035 (aromatic CH); 1600, 1545 (C=C, C=N),

Anal. Calcd. for $C_8H_5Cl_2N_3$: C, 44.89; H, 2.35; N, 19.63. Found: C, 45.11; H, 2.50; N, 19.42.

The aqueous solution from above was treated with sodium hydroxide (50%) to *p*H 6 to deposit **14** (4.5 g., 22% recovery).

4-Amino-2-chloro-6-methylpyrido[3,2-*d*]pyrimidine (**16**).

Ammonia was bubbled through a solution of **15** (3.85 g., 18.0 mmoles) in anhydrous dioxane (400 ml.) for 20 minutes at room temperature. The resulting mixture was evaporated to dryness, and the residue was triturated in water (300 ml.). The solid was collected by filtration and washed with water (2 x 100 ml.), yield 3.4 g. (97%), m.p. 256-257° dec. The crude product was recrystallized from boiling benzene (1000 ml.): yield 2.30 g. (66%); m.p. 251-252° dec.; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid 233 (22.7), 269 (4.9), 277 (4.8), 303 (6.51), 314 (19.3), 327 (8.2); *p*H 7–237 (21.9), 277 (5.6), 308 (4.9), 318 (6.2), 336 (4.9); $\bar{\nu}$ in cm^{-1}: 3440, 3270, 1630 (NH): 1600, 1570, 1540, 1515 (C=C, C=N).

Anal. Calcd. for $C_8H_7ClN_4$: C, 49.37; H, 3.62; N, 28.79. Found: C, 49.52; H, 3.67; N, 28.97.

4-[[3-(Diethylamino)propyl]amino]-2-chloro-6-methylpyrido-[3,2-*d*]pyrimidine Monohydrochloride (**17**).

A solution of 3-diethylaminopropylamine (1.30 g., 10.0 mmoles) in ethanol (50 ml.) was added to a mixture of **15** (2.14 g., 10.0 mmoles) in ethanol (50 ml.). After stirring at room temperature for 20 hours, the resulting solution was evaporated to dryness. The solid residue was triturated in ethyl ether (3 x 100 ml.), collected by filtration, and dried 4 hours at 100° *in vacuo* over phosphorus pentoxide, yield 3.10 g. (89%); m.p. 174-175°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid 283 (4.7), 307 (9.2), 319 (14.1), 334 (12.9); *p*H 7–281 (6.0), 322 (9.1), 336 (7.3); $\bar{\nu}$ in cm^{-1}: 3395, 1610 (NH); 1590, 1545 (C=C, C=N),

Anal. Calcd. for $C_{15}H_{22}ClN_5 \cdot HCl$: C, 52.33; H, 6.73; N, 20.34. Found: C, 52.04; H, 6.94; N, 20.42. Positive chloride test (7).

4-[[4-(Diethylamino)-1-methylbutyl]amino]-2-chloro-6-methyl-pyrido[3,2-*d*]pyrimidine Monohydrochloride (**18**).

A solution of 2-amino-5-diethylaminopentane (1.58 g., 10.0 mmoles) in ethanol (50 ml.) was added to a mixture of **15** (2.14 g., 10.0 mmoles) in ethanol (50 ml.). After stirring at room temperature for 22 hours, the resulting solution was evaporated to dryness. The dark red residual oil was triturated in ethyl ether (200 ml.), and the orange solid that formed was collected by filtration and dried at 100° for 4 hours *in vacuo* over phosphorus pentoxide, yield 3.30 g. (89%), m.p. 161-163° dec.; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid 275 (4.1), 310 (9.4), 322 (14.7), 336 (13.5); *p*H 7–285 (5.7), 325 (9.3), 338 (7.3); $\bar{\nu}$ in cm^{-1}: 3280, 1600 (NH); 1575, 1535 (C=C, C=N).

Anal. Calcd. for $C_{17}H_{26}ClN_5 \cdot HCl$: C, 54.84; H, 7.31; N, 18.81. Found: C, 54.62; H, 7.36; N, 18.56. Positive chloride test (7).

2,4-Bis[[4-(diethylamino)-1-methylbutyl]amino]-6-methylpyrido-[3,2-*d*]pyrimidine Trihydrochloride Hydrate (**19**).

A solution of 2-amino-5-diethylaminopentane (6.3 g., 40 mmoles) and **15** (2.1 g., 10 mmoles) in *N*,*N*-dimethylacetamide (50 ml.) was stirred at room temperature for 2.5 hours, then heated at reflux for 18 hours. The resulting solution was evaporated to dryness under reduced pressure, and the residue was extracted with ethyl ether (3 x 100 ml.). The ether extracts were combined and evaporated to dryness. The oily residue was dried *in vacuo*, dissolved in ethanol, and the resulting solution was treated with concentrated hydrochloric acid (3.8 ml., 45 mmoles). This solution was evaporated to dryness, and the residue was triturated repeatedly in ethyl ether. The solid that formed was collected by filtration and dried at room temperature *in vacuo* over phosphorus pentoxide, yield 4.2 g. (72%), m.p. indefinite, dec. from 80°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid 222 (29.9), 251 (17.4), 277 (8.0), 328 (9.0); *p*H 7–225 (27.1), 253 (16.8), 333 (6.7); $\bar{\nu}$ in cm^{-1}: 3230, 1635, 1625 (NH); 1570 (C=C, C=N).

Anal. Calcd. for $C_{26}H_{47}N_7 \cdot 3HCl \cdot H_2O$: C, 53.37; H, 8.96; N, 16.76. Found: C, 53.24; H, 10.17; N, 16.84.

Two years later the same sample was dried *in vacuo* over phosphorus pentoxide at 100°.

Anal. Calcd. for $C_{26}H_{47}N_7 \cdot 3HCl \cdot 3H_2O$: C, 17.15; N, 15.81. Found: Cl, 17.39; N, 15.66.

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REFERENCES

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(2) C. Temple, Jr., J. D. Rose, R. D. Elliott, and J. A. Montgomery, *J. Med. Chem.*, 11, 1216 (1968); *ibid.*, 13, 853 (1970).

(3) S. Shibasaki, *J. Pharm. Soc. Japan*, 71, 786 (1951).

(4) W. J. Irwin and D. G. Wibberly, *J. Chem. Soc., C*, 1745 (1967).

(5) For a description of the test procedures, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967).

(6) Insufficient compound was obtained for screening.

(7) A portion of the sample was extracted with 1 *N* sodium hydroxide, the extract was acidified with nitric acid, and the latter was treated with silver nitrate to give a precipitate of silver chloride.

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