Anal. Calcd for $C_5H_4ClN_5O \cdot H_2O$: C, 29.49; H, 2.97; Cl, 17.41; N, 34.39. Found: C, 29.52; H, 3.03; Cl, 17.60; N, 34.48.

The hydrate was dried at 110° *in vacuo* over P_2O_5 for 30 hr to again give anhydrous **13**, which exhibited carbonyl bands at 1740, 1720, and 1715 cm^{-1} in a KBr disk and at 1735 cm^{-1} in a 5% (w/v) solution in DMSO.

8-Amino-7-chloro-s-triazolo[1,5-c]pyrimidin-2(3H)-one (15) was prepared in 70% yield as previously described:[5] λ_{max}, mμ ($\epsilon \times 10^{-3}$), pH 7, 243 (30.0), 272 (6.89); $\bar{\nu}$, cm^{-1}, 1700, 1625, 1585, 1550, 1510; pmr, τ 4.62 (NH_2), 1.27 (CH), *ca.* −1.0 (NH).

Anal. Calcd for $C_5H_4ClN_5O$: C, 32.36; H, 2.17; Cl, 19.1; N, 37.73. Found: C, 32.47; H, 2.32; Cl, 19.1; N, 37.87.

6-Chloropurin-8(7H)-one (16).—Sodium nitrite (25 mg) was added with stirring to a suspension of **6** (50 mg) in H_2O containing 1 *N* HCl (0.5 ml). After 1 hr the precipitate of **16** was collected by filtration and dried *in vacuo* over P_2O_5: yield, 22 mg (48%). This material was identified by thin layer chromatography and by comparison of its ultraviolet and infrared spectra with those of authentic **16**.[5] In addition, **16** was the only ultraviolet absorbing material detected in a chromatogram of the reaction filtrate.

7-Chloro-8-ethoxymethyleneamino-s-triazolo[1,5-c]pyrimidin-2(3H)-one (18).—A suspension of **15** (300 mg) in diethoxymethyl acetate (10 ml) was stirred at room temperature for 40 hr, heated for 10 min on a hot water bath, and the resulting solution was cooled to deposit 70 mg of crude **18**: mp 249–253° dec with sublimation from 230°. The filtrate was diluted with EtOH and evaporated to dryness *in vacuo*. Recrystallization of the resulting residue from THF–petroleum ether (bp 85–105°) gave 250 mg of **18** (64%): mp 258–260° dec with sublimation from 230°. The total yield of **18** was 320 mg (82%): λ^{D}_{max}, mμ ($\epsilon \times 10^{-3}$), EtOH, 240 (19.2), 250 (19.4), 283 (8.15); $\bar{\nu}$, cm^{-1}, 1625, 1570, 1515.

Anal. Calcd for $C_8H_8ClN_5O_2$: C, 39.76; H, 3.33; Cl, 14.67; N, 28.98. Found: C, 40.16; H, 3.54; Cl, 14.60; N, 28.82.

Treatment of **18** with 0.1 *N* HCl at room temperature gave **15**.

8-Acetamido-7-chloro-s-triazolo[1,5-c]pyrimidin-2(3H)-one (19).—A suspension of **13** (1.44 g) in Ac_2O containing 1 drop of concentrated H_2SO_4 was stirred at room temperature for 1.5 hr. The solid (1.1 g) was collected by filtration and recrystallized first from THF–petroleum ether (bp 85–105°), then from EtOH: yield, 0.17 g (10%); mp >264°; λ^{D}_{max}, mμ ($\epsilon \times 10^{-3}$), pH 7, 235 (39.4), 275 (sh) (3.72), 308 (3.65); $\bar{\nu}$, cm^{-1}, 1685 1650, 1575, 1540, 1500; pmr, τ 7.85 (CH_3), 0.62 (CH), −0.13 and −0.55 (NH).

Anal. Calcd for $C_7H_6ClN_5O_2$: C, 36.93; H, 2.65; Cl, 15.6; N, 30.76. Found: C, 36.91; H, 2.90; Cl, 15.8; N, 30.76.

Registry No.—**1**, 15152-49-5; **4**, 15128-97-9; **5**, 15128-96-8; **6**, 15128-98-0; **7**, 15206-32-3; **8**, 15128-99-1; **11**, 15180-19-5; **12**, 15129-00-7; **13**, 15206-33-4; **15**, 15129-01-8; **18**, 15129-02-9; **19**, 15129-03-0.

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Potential Folic Acid Antagonists. III. Deaza Analogs of Methotrexate. III. 1- and 3-Deaza Analogs of 2,4-Diamino-6-[(N-methylanilino)methyl]pteridine[1,2]

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The reaction of 1-amino-3-(N-methylanilino)-2-propanol with diethyl 4-chloro-3-nitro-2,6-pyridinedicarbamate (**1**) and ethyl 4-amino-6-chloro-5-nitro-2-pyridinecarbamate (**8**), respectively, gave the corresponding 2-hydroxy-3-(N-methylanilino)propylaminopyridines **2** and **9**. Oxidation of these alcohols to the corresponding 3-(N-methylanilino)-2-oxopropylaminopyridines **4** and **12** was accomplished with dimethyl sulfoxide and N,N′-dicyclohexylcarbodiimide (Pfitzner–Moffatt procedure). Reductive cyclization of these 2-oxopropylaminopyridines followed by ring oxidation with potassium permanganate and basic hydrolysis of the urethan groups provided 5,7-diamino-3-[(N-methylanilino)methyl]pyrido[3,4-*b*]pyrazine (**14**) and 6,8-diamino-2-[(N-methylanilino)methyl]pyrido[2,3-*b*]pyrazine (**17**), the 1- and 3-deaza analogs of 2,4-diamino-6-[(N-methylanilino)methyl]pteridine.

Continuation of our studies on the structural requirements for binding to and, therefore, inhibiting the enzymes involved in folic acid metabolism prompted the synthesis of 5,7-diamino-3-[(N-methylanilino)-methyl]pyrido[3,4-*b*]pyrazine (**14**) and 6,8-diamino-2-[(N-methylanilino)methyl]pyrido[2,3-*b*]pyrazine (**17**), the 1- and 3-deaza analogs of 2,4-diamino-6-[(N-methylanilino)methyl]pteridine. In earlier papers the unambiguous synthesis of diamino 1- and 3-deazapteridines from pyridine intermediates containing adjacent chloro and nitro groups involved, respectively, the replacement of the chloro group with an α-amino ketone moiety, reductive cyclization, and oxidation.[2,3] Apparently this route is limited only by the availability of the α-amino ketone. Although procedures for the preparation of 1,3-diamino-2-propanols are well known,[4] a method for the oxidation of these alcohols to the corresponding 1,3-diaminoacetones has not been reported. The successful preparation of **14** and **17** involved as a key step the oxidation of a complex 2-hydroxy-3-(N-methylanilino)propylaminopyridine to the corresponding 3-(N-methylanilino)-2-oxopropylaminopyridine.

Reaction of the chloropyridine **1** with 1-amino-3-(N-methylanilino)-2-propanol[4] gave **2**, which was hydrogenated in the presence of Raney nickel to give the 3-aminopyridine **3**. The intramolecular cyclization of the latter to the tetrahydro derivative **5** under a variety of neutral and acidic conditions[5] was unsuccessful. When **3** was heated in refluxing propanol, ring closure occurred between the 3-amino and the 2-urethan groups to give **6**. The avoid this type of ring closure, oxidation of the secondary alcohol moiety of the propyl

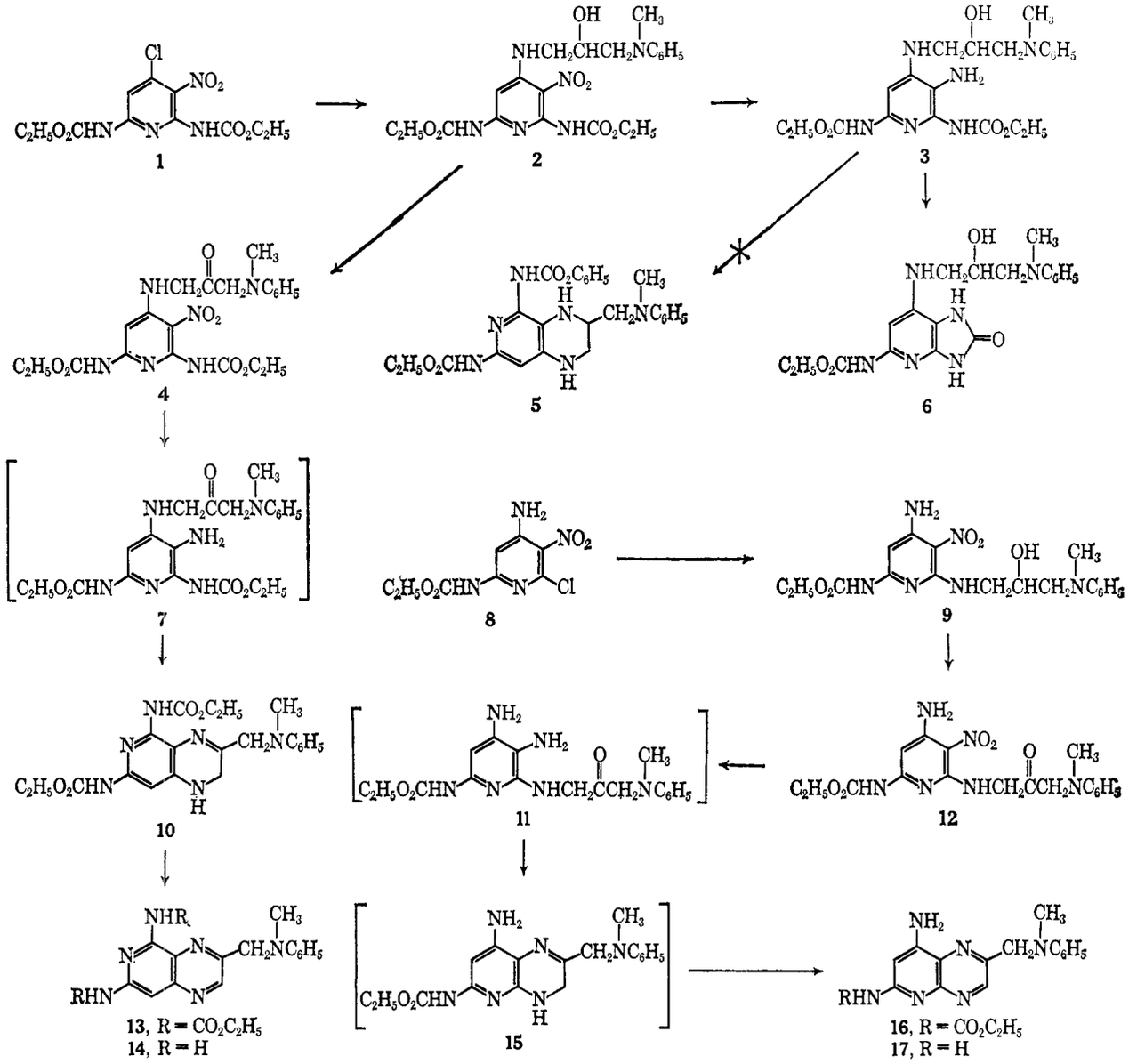
(1) This work was supported by funds from the C. F. Kettering Foundation and from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51.

(2) For the second paper in this series, see R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 1890 (1966).

(3) J. A. Montgomery and N. Wood, *ibid.*, **29**, 734 (1964).

(4) O. Eisleb, German Patent 473,219 (Aug 1926); *Chem. Zentr.*, **100** (II), 350 (1929).

(5) S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 859 (1964); M. G. Reinecke and L. R. Kray, *ibid.*, **29**, 1736 (1964).



side chain of **2** to the 3-(N-methylanilino)-2-oxopropylaminopyridine **4** was attempted. Although no reaction was observed when **2** was treated with aluminum isopropoxide in acetone, treatment of **2** with chromic anhydride in pyridine[6] gave a product which analyzed correctly for the ketone **4**. The absence of an N-methyl band in the proton magnetic resonance spectrum of this product, however, indicated that the reagent had reacted with the N-methyl group rather than the alcohol moiety. Preferential oxidation of the alcohol group of **2**, however, was effected with N,N'-dicyclohexylcarbodiimide, dimethyl sulfoxide, and phosphoric acid[7] to give the desired ketone **4**. Hydrogenation of **4** over Raney nickel gave **7**, which underwent spontaneous ring closure. The resulting crude dihydro derivative **10** was oxidized with potassium permanganate in acetone to give **13**, which was purified by recrystallization. The urethan groups of **13** were cleaved with potassium hydroxide in ethanol to give the 1-deazapteridine **14**, isolated as the one-third ethanolate. The ethanol content in this sample was confirmed both by elemental analysis and by comparison of the integrated intensities of the peaks in the proton magnetic resonance spectrum in DMSO-d_6. When this sample was dried at an elevated temperature, decomposition appeared to occur. Synthesis of the diamino-3-deazapteridine **17** was achieved by a route similar to that used in the preparation of **14**. Replacement of the chlorine atom of the 6-chloropyridine **8**[2] with 1-amino-3-(N-methylanilino)-2-propanol gave **9**, which was oxidized to the 2-oxopropylaminopyridine **12**. Hydrogenation of the nitro group of **12** resulted in spontaneous cyclization of the intermediate diamine **11** to give the dihydrodeazapteridine **15**. Oxidation of **15** with potassium permanganate in acetone gave the 3-deazapteridine **16**. The urethan group of the latter was removed with alcoholic potassium hydroxide to give the chromatographically pure diamino-3-deazapteridine **17**.

(6) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

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Experimental Section

Melting points, unless otherwise indicated, were determined on a Kofler Heizbank and are corrected. The ultraviolet absorption spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer (sh designates shoulder), and the infrared absorption spectra were determined in pressed potassium bromide

disks with a Perkin-Elmer Model 521 spectrophotometer. The proton magnetic resonance spectra were obtained with a Varian A-60 or A-60A spectrometer at a probe temperature of about 40° using tetramethylsilane as internal reference.

Diethyl 4-[2-Hydroxy-3-(N-methylanilino)propylamino]-3-nitro-2,6-pyridinedicarbamate (2).—A solution of **1** (10.0 g, 30.1 mmoles), 1-amino-3-(N-methylanilino)-2-propanol[4] (5.68 g, 31.5 mmoles), and triethylamine (6.09 g, 60.2 mmoles) in methanol (10 ml) was allowed to stand at room temperature for 2 days and then refrigerated. The resulting orange precipitate was collected by filtration, washed with methanol (15 ml), and recrystallized from ethanol (150 ml). The yellow product was collected by filtration and dried at 65° *in vacuo* over P_2O_5 to yield 10.1 g (70 %): mp 114° dec; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1, 225 (26.8), 253 (27.4), 276 (17.0), 333 (10.8), pH 7 (unstable), 226, 251, 360, pH 13 (unstable), 243, 302, 375; $\bar{\nu}$ 3380 (NH, OH), 3100–2850 (CH), 1740 (C=O), 1610, 1550, 1490 (ring stretching), 1570 (sh), 1290 (NO_2), 1200 (C–O–C), 743, 688 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{21}H_{28}N_6O_7$: C, 52.93; H, 5.92; N, 17.64. Found: C, 52.73; H, 5.95; N, 17.42.

Diethyl 3-Amino-4-[2-hydroxy-3-(N-methylanilino)propylamino]-2,6-pyridinedicarbamate (3).—A suspension of finely powdered **2** (500 mg, 1.05 mmoles) in ethanol (50 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel (790 mg, weighed wet with ethanol). In 4 hr the solution had taken up the theoretical amount of hydrogen and was filtered under N_2. Three crops of crude **3** were obtained from the filtrate by addition of petroleum ether (bp 65–85°) and refrigeration. The crystals were collected by filtration under N_2 and dried *in vacuo* over P_2O_5 to yield 386 mg, mp 163–167°. Recrystallization of the crude product from 1:1 ethanol–petroleum ether (65–85°) (20 ml) gave pure **3** in 71% yield: mp 167°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1, 239 (37.6), 270 (sh) (12.2), 298 (9.8), pH 7, 234 (40.2), 252 (sh) (23.4), 292 (8.15), pH 13, 236 (unstable), 252 (sh) (25.7), 296 (9.80); $\bar{\nu}$ 3420, 3360, 3320 (NH, OH), 2980, 2935, 2910, 2870 (CH), 1730, 1690 (C=O), 1615 (NH_2), 1600, 1545, 1505 (ring stretching), 1215 (C–O–C), 740, 685 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{21}H_{30}N_6O_5$: C, 56.49; H, 6.78; N, 18.82. Found: C, 56.32; H, 6.68; N, 18.92.

Diethyl 4-[3-(N-Methylanilino)-2-oxopropylamino]-3-nitro-2,6-pyridinedicarbamate (4).—Crystalline *o*-phosphoric acid (1.82 g, 18.6 mmoles) was added to a solution of **2** (4.77 g, 10.0 mmoles) and N,N′-dicyclohexylcarbodiimide (6.19 g, 30.0 mmoles) in anhydrous dimethyl sulfoxide (50 ml). The initially exothermic reaction was maintained at room temperature for 2 hr, filtered to remove N,N′-dicyclohexylurea, and diluted with water (100 ml). The solid that deposited was collected by filtration, washed with ethanol (10 ml), and extracted with boiling methanol (200 ml). Refrigeration of the extract gave a yellow crystalline solid which was collected by filtration, dissolved in hot benzene (6 ml), and filtered. The filtrate deposited crystalline **4** which was collected by filtration, washed with 1:2 benzene–ethanol (15 ml), and dried *in vacuo* over P_2O_5 to yield 2.12 g (45%): indefinite melting point; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1, 208 (sh) (21.0), 224 (25.3), 250 (26.0), 276 (14.1), 333 (10.4), pH 7 (unstable), 204, 224, 253, 356, pH 13 (unstable), 235, 293, 353; $\bar{\nu}$ 3430, 3340, 3250 (sh) (NH), 3060, 2980, 2920, 2820 (CH), 1740 (C=O), 1615, 1575, 1510, 1490 (ring stretching), 1550, 1290 (NO_2), 1205 (C–O–C), 748, 693 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{21}H_{26}N_6O_7 \cdot {}^1/_2H_2O$: C, 52.17; H, 5.63; N, 17.38. Found: C, 51.90; H, 5.81; N, 17.22.

Ethyl 7-[2-Hydroxy-3-(N-methylanilino)propylamino]imidazo[4,5-*b*]pyridin-2(3H)-one-5-carbamate (6).—A solution of **3** (500 mg, 1.12 mmoles) in 1-propanol (50 ml) was heated at reflux temperature for 3 hr under N_2. Refrigeration of the solution gave white crystals which were collected by filtration, dried *in vacuo* over P_2O_5, and recrystallized from ethanol (200 ml) to yield 393 mg (88%): mp >280° (Kofler Heizbank); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1, 243 (35.7), 275 (14.2), 303 (18.8), pH 7, 236 (39.4), 254 (sh) (22.4), 287 (15.8), pH 13, 237 (38.6), 296 (18.3); $\bar{\nu}$ 3380, 3330 (sh), 3130 (sh) (NH, OH), 2975, 2945, 2700 (CH), 1710, 1697 (C=O), 1640, 1600, 1540, 1506 (ring stretching), 1218 (C–O–C), 743, 688 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{19}H_{24}N_6O_4$: C, 56.99; H, 6.04; N, 20.99. Found: C, 56.95; H, 6.14; N, 21.07.

Ethyl 4-Amino-6-[2-hydroxy-3-(N-methylanilino)propylamino]-5-nitro-2-pyridinecarbamate (9).—A mixture of **8**[2] (5.84 g, 22.4 mmoles), 1-amino-3-(N-methylanilino)-2-propanol (4.24 g, 23.5 mmoles), triethylamine (4.53 g, 44.8 mmoles), and methanol (60 ml) was stirred under N_2 in an oil bath at 55° for 16 hr. Upon cooling the reaction mixture in an ice bath a yellow crystalline product separated and was collected by filtration, washed with cold ethanol, and dried *in vacuo* over P_2O_5 to yield 6.50 g, mp 146°. The residue obtained by evaporation of the filtrate was triturated in water and recrystallized from methanol to give an additional 1.08 g of **10**, mp 142°. The total yield was 7.58 g (84%). The analytical sample was obtained by recrystallization of a portion of the product from methanol: mp 147; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1, 221 (28.5), 233 (sh) (22.7), 265 (sh) (8.92), 346 (11.3), pH 7, 240 (sh) (18.6), 252 (20.0), 346 (11.3), pH 13, 252 (20.3), 349 (12.7); $\bar{\nu}$ 3460, 3355, 3185, 3130 (sh) (NH, OH), 2975, 2925, 2870 (CH), 1740 (C=O), 1610 (NH_2), 1600 (sh), 1505, 1492 (ring stretching), 1555, 1320 (NO_2), 1210 (C–O–C), 745, 690 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{18}H_{24}N_6O_5$: C, 53.45; H, 5.98; N, 20.78. Found: C, 53.57; H, 6.12; N, 20.73.

Ethyl 4-Amino-6-[3-(N-methylanilino)-2-oxopropylamino]-5-nitro-2-pyridinecarbamate (12).—Crystalline *o*-phosphoric acid (274 mg, 2.79 mmoles) was added to a solution of **9** (250 mg, 0.619 mmoles) and N,N′-dicyclohexylcarbodiimide (383 mg, 1.86 mmoles) in anhydrous dimethylsulfoxide (3 ml). The initially exothermic reaction was maintained at room temperature for 2 hr, filtered to remove N,N′-dicyclohexylurea, and diluted with cold water (10 ml). The precipitate of crude product was collected by filtration, washed with cold water, and dried *in vacuo* over P_2O_5 to yield, 180 mg (72%). This material was purified on a thick layer chromatogram of silica gel H by development with 5:1 chloroform–ethyl acetate. Evaporation of a methanol extract of the principal yellow band and recrystallization of the resulting residue from hot benzene (5 ml) gave yellow needles which were collected by filtration, washed with benzene, and dried at 100° *in vacuo* over P_2O_5 to yield 36 mg (14%): mp 182° dec; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1 (unstable), 217 235 (sh), 243, pH 7, 242 (20.7), 244 (12.4), pH 13, 232 (sh) (20.4), 248 (12.8); $\bar{\nu}$ 3440, 3384, 3325 (NH), 2978, 2920, 2847 (CH), 1728, 1713 (C=O), 1615 (NH_2), 1600, 1487 (ring stretching), 1550, 1310 (NO_2), 1200 (C–O–C), 735, 679 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{18}H_{22}N_6O_5$: C, 53.72; H, 5.51; N, 20.89. Found: C, 53.94; H, 5.70; N, 20.99.

Purification of the crude product on another run (18.7 mmoles) was attempted by column chromatography (90 g of silica gel H). Crystallization of the product on the column while eluting with 9:1 chloroform–ethyl acetate resulted in isolation of a slightly impure product, mp 164° in 24% yield. This material was used without further purification in the synthesis of **15**.

Diethyl 3-[(N-Methylanilino)methyl]pyrido[3,4-*b*]pyrazine-5,7-dicarbamate (13).—A solution of **4** (650 mg, 1.37 mmoles) in ethyl acetate (20 ml) was stirred with Raney nickel (1.1 g, weighed wet with ethanol) in the presence of hydrogen at room temperature and atmospheric pressure for 16 hr. The resulting solution was filtered under N_2 and evaporated to dryness *in vacuo*. The residue of crude **10** was dissolved in acetone (70 ml) and treated dropwise with a 0.27% solution of potassium permanganate in acetone until the color of the permanganate persisted (about 65 ml was required). The solution was filtered to remove manganese dioxide and evaporated *in vacuo* to give a red oil. A solution of this oil in ethanol precipitated a red impurity which was removed by filtration. Evaporation of the filtrate *in vacuo* gave a red residue which was recrystallized from 1:1 benzene–petroleum ether (bp 30–60°) (4 ml). The resulting orange crystalline product was collected by filtration and dried at 78° *in vacuo* over P_2O_5 to yield 284 mg (49%): mp 173°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1, 263 (33.9), 308 (10.6), 393 (4.76), pH 7 (unstable), 261, 295 (sh), 382, pH 13, 260 (36.3); $\bar{\nu}$ 3380, 3270 (NH), 2980, 2955, 2925, 2910 (CH), 1755, 1743 (C=O), 1618, 1600, 1555 (SH), 1530 (sh), 1508 (ring stretching), 1215, 1195 (C–O–C), 744, 690 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{21}H_{24}N_6O_4$: C, 59.42; H, 5.70; N, 19.80. Found: C, 59.43; H, 5.78; N, 19.79.

5,7-Diamino-3-[(N-methylanilino)methyl]pyrido[3,4-*b*]pyrazine (14).—A solution of **13** (404 mg, 0.953 mmole) and KOH (2.67 g, 47.6 mmoles) in ethanol (42 ml) was refluxed under N_2 for 6 hr. The reaction mixture was evaporated to near dryness *in vacuo* and treated dropwise at 0° with 3 *N* HCl (10 ml). The resulting red precipitated was collected by filtration, washed with cold water, and dried *in vacuo* over P_2O_5 to yield 191 mg (68%): mp 195° dec; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1 (unstable), 249, 328,

pH 7 and 13 (unstable), 252, 267, 317; $\bar{\nu}$ 3490, 3380, 3313, 3140 (NH), 2990–2700 (CH), 1648 (NH_2), 1592, 1577, 1520, 1497 (ring stretching), 750, 683 cm^{-1} (monosubstituted phenyl); pmr (4% DMSO-d_6 w/v), 1.53 (2-H), 3.15 (phenyl), ~3.33 (NH_2), ~4.15 (NH_2), 4.10 (8-H), 5.35 (CH_2), 6.92 (CH_3), (ethanol, 6.58 (CH_2), 8.93 (CH_3)).

Anal. Calcd for $C_{15}H_{16}N_6 \cdot {}^1/_3C_2H_6O$: C, 63.63; H, 6.14; N, 28.43. Found: C, 63.59; H, 6.20; N, 28.51.

Ethyl 8-Amino-2-[(N-methylanilino)methyl]pyrido[2,3-*b*]pyrazine-6-carbamate (16).—A suspension of crude **12** (1.45 g, 3.60 mmoles) in ethanol (70 ml) was stirred with Raney nickel (3.0 g weighed wet with ethanol) in the presence of hydrogen at room temperature and atmospheric pressure for 16 hr. The resulting solution was filtered under N_2, and evaporated to dryness under reduced pressure. The residue was redried *in vacuo* over P_2O_5 to give **ethyl 8-amino-3,4-dihydro-2-[(N-methylanilino)-methyl]pyrido[2,3-*b*]pyrazine-6-carbamate (15)**: mp *ca.* 115° with softening from 107° (Mel-Temp); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1, 232 (24.2), 265 (sh) (9.81), 317 (10.1), pH 7, 225 (32.5), 245 (sh) (24.8), 331 (8.13), pH 13, 245 (sh) (24.5), 332 (8.21); $\bar{\nu}$ 3500–3100 (NH), 2970, 2920, 2848 (CH), 1730 (C=O), 1615 (NH_2), 1595, 1535, 1500 (ring stretching), 1200 (C–O–C), 742, 685 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{18}H_{22}N_6O_2 \cdot {}^1/_4C_2H_6O$: C, 60.72; H, 6.47; N, 22.97. Found: C, 60.68; H, 6.64; N, 22.95.

A stirred solution of the above-described solid (**15**) in acetone (70 ml) was treated dropwise with a 0.27% solution of potassium permanganate in acetone until the color of permanganate persisted (about 150 ml was required). The solution was filtered to remove manganese dioxide and evaporated to dryness *in vacuo*. The residue was crystallized from ethanol (100 ml) to give yellow platelets of **16** which were collected by filtration, washed with cold ethanol, and dried at 135° *in vacuo* over P_2O_5 to yield 950 mg (75%): mp >350° (darkens from 280°); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1, 225 (19.1), 258 (7.32), 327 (11.0), pH 7, 220 (18.7), 265 (18.0), 333 (6.87), pH 13, 228 (13.6), 266 (16.4), 336 (6.25); $\bar{\nu}$ 3445, 3315, 3235, 3190 (NH), 3092, 3052, 2981, 2970, 2920 (CH), 1696 (C=O), 1623 (NH_2), 1588, 1570, 1546, 1533, 1504 (ring stretching), 1230 (C–O–C), 737, 685 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{18}H_{20}N_6O_2$: C, 61.35; H, 5.72; N, 23.85. Found: C, 61.08; H, 5.64; N, 24.19.

6,8-Diamino-2-[(N-methylanilino)methyl]pyrido[2,3-*b*]pyrazine (17).—A solution of **16** (200 mg, 0.475 mmole) and KOH (670 mg, 12.0 mmoles) in ethanol (10 ml) was refluxed under N_2 for 7 hr. The reaction mixture was diluted with water (4 ml), cooled to 0°, and acidified with 6 *N* HCl to pH 3. This mixture was warmed and the resulting solution was filtered and carefully adjusted to pH 8 with 50% aqueous sodium hydroxide. After cooling the mixture in an ice bath, the yellow precipitate of **17** was collected by filtration under N_2, washed with cold water (2 ml), and dried *in vacuo* over P_2O_5 to yield 110 mg (73%) mp *ca.* 153–157°. Elemental analysis indicated that this product was a partial hydrochloride, partial hydrate. A portion of the product (100 mg) was purified by trituration with water (2 ml) containing 1 *N* NaOH (0.32 ml). The resulting solid was collected by filtration, washed with water, and dried at 65° *in vacuo* over P_2O_5 to yield 81.0 mg: mp *ca.* 79–86° (Mel-Temp); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1, 225 (39.5), 245 (sh) (8.94), 339 (15.9), pH 7, 221 (35.8), 249 (20.1), 343 (12.3), pH 13, 261 (23.6), 355 (10.7); $\bar{\nu}$ 3600–2400 (NH, OH, CH), 1620 (NH_2), 1595, 1530, 1503 (ring stretching), 747, 688 cm^{-1} (monosubstituted phenyl); pmr (5% DMSO-d_6 w/v), τ 1.50 (3-H), 3.12 (phenyl), 3.60 (NH_2), 3.92 (7-H), 5.26 (CH_2), 6.85 (CH_3).

Anal. Calcd for $C_{15}H_{16}N_6$: C, 64.27; H, 5.75; N, 29.98. Found: C, 64.02; H, 5.98; N, 29.98.

Registry No.—Folic acid, 59-30-3; **2**, 15223-95-7; **3**, 15223-96-8; **4**, 15223-97-9; **6**, 15223-98-0; **9**, 15223-99-1; **12**, 15275-66-8; **13**, 15224-00-7; **14**, 15224-01-8; **15**, 15224-02-9; **16**, 15224-03-0; **17**, 15224-04-1.

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Azetidines. II.[1] The Synthesis and Stevens Rearrangement of 2-Phenyl-1,1,3,3-tetramethylazetidinium Iodide[2,3]

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The title compound (**2**) was synthesized by two routes. 1-Chloro-2,2-dimethyl-3-dimethylamino-1-phenylpropane (**5**), prepared from 2,2-dimethyl-3-dimethylaminopropanol (**3**) *via* 2,2-dimethyl-3-dimethylamino-1-phenyl-1-propanol (**4**), gave **2** when treated with sodium iodide. Methyl-3-bromo-2,2-dimethyl-3-phenylpropylammonium bromide (**8**) was obtained from the benzamide (**9**) of 2,2-dimethyl-3-methylaminopropanal (**6**) *via* 2,2-dimethyl-3-(N-methylbenzamido)-1-phenyl-1-propanol (**10**) and 2,2-dimethyl-3-methylamino-1-phenyl-1-propanol (**7**). Treatment of **8** with aqueous hydroxide gave fragmentation products plus 2-phenyl-1,3,3-trimethylazetidine (**1**), which reacted with methyl iodide to form **2**. Reaction of **2** with phenyllithium gave 1-dimethylamino-2,2-dimethyl-3,3-diphenylpropane (**11**), 2-phenyl-1,2,3,3-tetramethylazetidine (**12**), plus small amounts of **1** and two compounds tentatively identified as rearrangement products. Reaction of **2** with potassium amide in liquid ammonia gave 2,2-dimethyl-3-dimethylaminopropiophenone (**15**), 4,4-dimethyl-3-dimethylamino-5-phenyl-2-isoxazoline (**16**), and small amounts of rearrangement products.

Relatively few azetidines or azetidinium salts have been prepared by direct ring closure,[4-6] probably because of the occurrence of competing reactions which can preclude formation of the four-membered ring. One of these, which has been called "fragmentation" and has been studied extensively by Grob and coworkers,[7] was observed in the preparation of **1** and in the thermal decomposition of **2**.

(1) Part I: A. G. Anderson, Jr., and M. T. Wills, *J. Org. Chem.*, **32**, 3241 (1967).

(2) From the Ph.D. Thesis of M. T. Wills, University of Washington, Seattle, Wash.

(3) Supported in part by State of Washington Initiative 171 Funds for Research in Biology and Medicine.

(4) For a recent review, see J. A. Moore, "The Chemistry of Heterocyclic Compounds," Vol. 10, part II, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter VII.

(5) The method of Wadsworth, *J. Org. Chem.*, **32**, 1184 (1967), appeared after the present work was completed.

(6) V. R. Gaertner, *Tetrahedron Letters*, 4691 (1966); V. R. Gaertner, *ibid.*, 343 (1967); N. H. Cromwell and E. Doomes, *ibid.*, 4037 (1966); J. L. Imbach, E. Doomes, R. P. Rebman, and N. H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967).

(7) C. A. Grob and P. W. Schiess, *Angew. Chem.*, **79**, 1 (1967); C. A. Grob, "Kekule Symposium on Theoretical Chemistry," Butterworth and Co. Ltd., London, 1959, pp 114–127.