and concentrated to yield an oil. This oil was taken up in ether, an equal volume of petroleum ether (bp 30–60°) was added, and the solution was cooled; 70 mg (49%) of **4** separated, mp 79–80.5°.

Anal. Calcd for $C_6H_{14}N_2O_2S$: C, 40.43; H, 7.92; N, 15.72. Found: C, 40.25; H, 7.95; N, 15.43.

The spectral characteristics of **4** are as follows: ir (Nujol) 3360 (strong, NH), 1350, 1160, 1135, and 1120 cm^{-1} (strong, SO_2); nmr ($CDCl_3$) δ 3.80–2.67 (m, 6, ring protons), 2.33 [s, 6, $-N(CH_3)_2$], and 1.67 (broad, 2, $-NH_2$).

2,2,5,5-Tetradeuteriothiophene 1,1-Dioxide (5).—This compound was prepared according to the method of Weinberg, *et al.*[6] 2,5-Dihydrothiophene 1,1-dioxide (1.18 g, 9.98 mmol) was dissolved in tetrahydrofuran (10 ml); to this solution was added deuterium oxide (20.4 g, 99.7%, Merck Sharp and Dohme of Canada, Ltd.) and anhydrous potassium carbonate (0.5 g). The mixture was stirred for 2 days at room temperature. Solvent was removed under vacuum. Deuterium oxide (13 g) and tetrahydrofuran (7 ml) were added and the procedure was repeated. Solvent was then removed. The residue was triturated with chloroform, and the chloroform was dried ($MgSO_4$), filtered, and evaporated to yield 0.945 g (77.5%) of **5**, mp 63–64°. The nmr spectrum showed greater than 95% deuterium incorporation: nmr ($CDCl_3$) δ 6.05 (s).

***trans*-3-Bromo-3,4-dihydro-4-succinimido-2,2,5,5-tetradeuteriothiophene 1,1-Dioxide (6).**—Compound **5** (820 mg, 6.71 mmol), N-bromosuccinimide (670 mg, 3.76 mmol) and benzoyl peroxide (570 mg) were refluxed in carbon tetrachloride (15 ml) for 3 hr. The solution was then cooled and filtered. The collected solid material was taken up in chloroform and the solution was filtered. The filtrate was concentrated, methanol was added and heated, and the hot solution was filtered. Upon cooling, the filtrate deposited light yellow crystals. Recrystallization from methanol gave white needles: mp 214–215°; nmr (DMSO-d_6) δ 5.10 (two resolved signals which are separated by 2 cps, two hydrogens on C_3 and C_4) and 2.77 [s, 4, $-C(O)CH_2CH_2C(O)-$].

Registry No.—**1**, 77-79-2; **2**, 23740-31-0; **3**, 23740-32-1; **4**, 23740-33-2; **5**, 20966-34-1; **6**, 23829-44-9; N-bromosuccinimide, 128-08-5.

Acknowledgment.—We are grateful to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (Grant 1061-G).

Potential Folic Acid Antagonists. IV. Synthetic Approaches to Analogs of Aminopterin and Methotrexate. IV. The Preparation of *p*-{[(2,4-Diamino-6-pteridinyl)methyl]amino}-benzoic Acids[1,2]

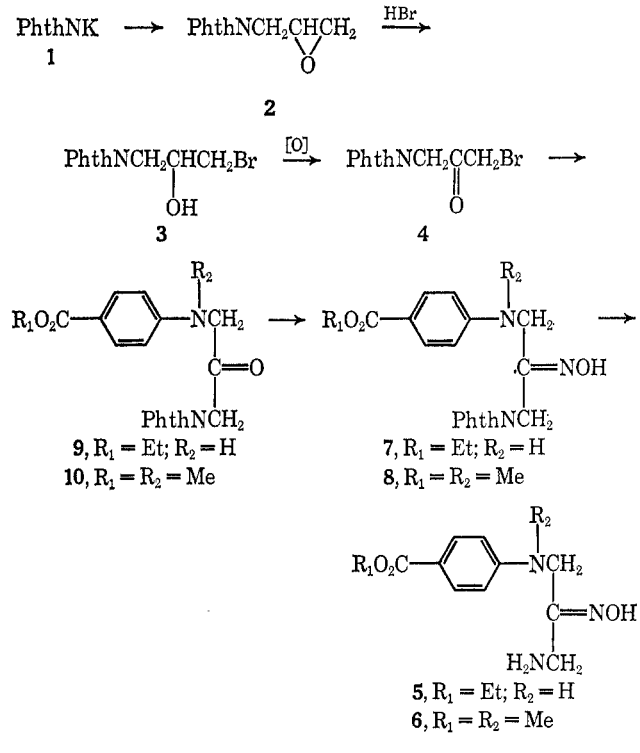
ROBERT D. ELLIOTT, CARROLL TEMPLE, JR., AND JOHN A. MONTGOMERY

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received October 27, 1969

As part of our program on the synthesis of folic acid antagonists, methods were needed for the construction of the pyrazine ring containing the *p*-(methyleneamino)-benzoyl moiety of folic acid, and of its analogs aminopterin and methotrexate. Although the preparation of the pteroic acid analogs **21**[3] and **23**[4] by the reaction of 2,4,5,6-tetraaminopyrimidine with a *p*-aminobenzoic acid in the presence of a halogenated three-carbon aldehyde or ketone has been reported, the former was obtained in a crude mixture and the latter as a dihydrate in unspecified yield. This method of preparation is unattractive in that the desired product is obtained in low yield and is difficult, if not impossible, to purify. Previously, Boon and Leigh[5] developed an unambiguous route to 6-substituted pteridines that involved the reduction of [(5-phenylazo-4-pyrimidinyl)amino]acetones. However, the synthesis by this method of a 6-(phenoxymethyl)pteridine for use as an intermediate for the preparation of compounds like **21** and **23** was unsuccessful when the phenoxy group underwent reductive cleavage. We report the preparation of some *p*-{[(2,4-diamino-6-pteridinyl)methyl]amino}benzoic acids by a modification of the Boon and Leigh procedure, which will also be used to prepare other analogs in which the pyrimidine ring has been replaced with the pyridine ring to give the corresponding 1- and 3-deazapteridine ring systems.

The intermediate N-3-(bromoacetonyl)phthalimide (**4**) was prepared in three steps in 24% yield from potassium phthalimide (**1**) *via* **2** and **3**.[6] Alkylation of



Phth = phthaloyl

ethyl *p*-aminobenzoate and methyl *p*-(methylamino)-benzoate,[7] respectively, with the bromo ketone **4** gave the diaminoacetones **9** (72%) and **10** (34%). The condensation of these keto compounds with $NH_2OH \cdot HCl$ in a refluxing mixture of pyridine and EtOH gave the corresponding oximes **7** (43%) and **8** (72%), both isolated as a mixture of the *syn* and *anti* isomers. The

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

(2) For a related paper in this series, see R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **33**, 533 (1949).

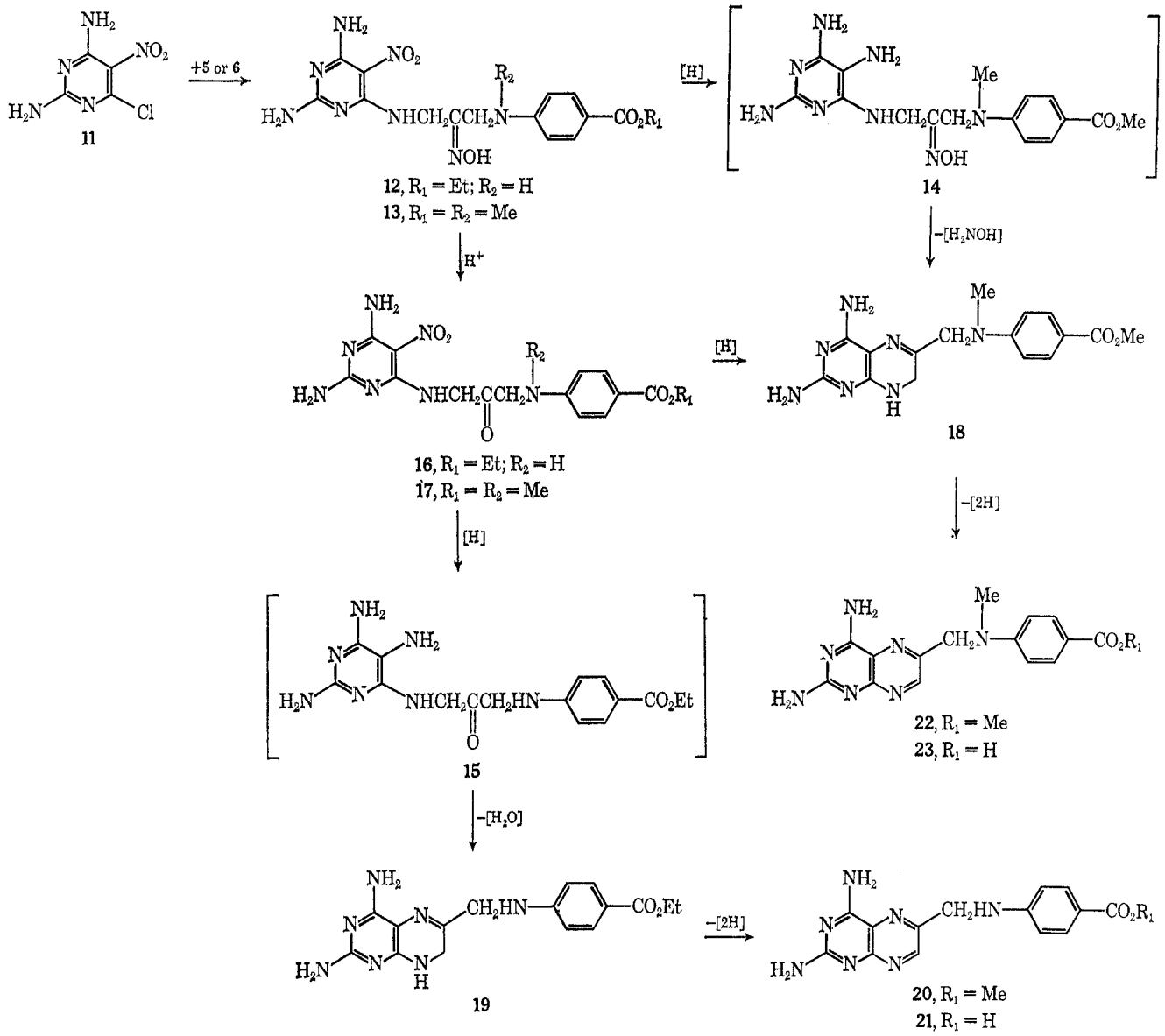
(3) D. R. Seeger, U. S. Patent 2,568,597 (1947).

(4) D. R. Seeger, D. B. Cosulich, J. M. Smith, Jr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, **71**, 1753 (1949).

(5) W. R. Boon and T. Leigh, *J. Chem. Soc.*, 1497 (1951).

(6) D. P. Tschudy and A. Collins, *J. Org. Chem.*, **24**, 556 (1959).

(7) F. Klaus and O. Baudisch, *Ber.*, **51**, 1044 (1918).



phthaloyl protecting group of **7** and **8**, respectively, was cleaved with anhydrous N_2H_4 in EtOH to give the oximes of the diaminoacetones **5** (72%) and **6** (71%).

The known 2,4-diamino-6-chloro-5-nitropyrimidine (**11**) was prepared by the nitration of 2,4-diamino-6-chloropyrimidine.[8] The alkylation of the aminoacetone oxime **5** with **11** was carried out in ethanolic Et_3N to give a homogeneous sample of the 3-[(4-pyrimidinyl)-amino]acetone oxime **12** (tlc). The latter was not purified but was hydrolyzed with HCl to give the hydrochloride of the 3-[(4-pyrimidinyl)amino]acetone **16**. The nitro group of the latter was reduced with Raney nickel in a large volume of EtOH, and the resulting 5-aminopyrimidine (**15**) was cyclized *in situ* to give the 7,8-dihydropteridine **19**. This product analyzed correctly for **19**, but its tlc indicated the presence of a trace amount of the heteroaromatic pteridine **20**. Oxidation of this material with $KMnO_4$ in Me_2CO gave a pure sample of the heteroaromatic compound **20**. Hydrolysis of the ester moiety of the latter to the benzoic acid **21** was attempted with NaOH in DMSO, but this reaction appeared to give only decomposition products.[9] Also treatment of **20** with NaOAc in HOAc for an extended period of time provided an eight-component mixture containing **20** (tlc). The conversion of **20** to **21** was also attempted by transesterification with refluxing HCO_2H, but this reaction resulted in formylation of the amino groups without affecting the ester function (pmr).

The alkylation of **6** with the chloropyrimidine **11** gave the oxime **13** (91%), which was treated with HCl to give **17** (75%). The hydrogenation of **17** in the presence of Raney nickel in EtOH gave the dihydropteridine **18** (39%). However, this reduction required a long period of time (6 days), which was attributed to the low solubility of ketone **17** in EtOH.

Another route to **18** involved the reduction of the nitro group of the oxime **13**. The reduction mixture from this hydrogenation gave an analytically pure sample of the dihydropteridine **18**, *in situ* cyclization presumably resulting from a transamination-type reaction between the pyrimidine 5-amino group and the side-chain oxime function of **14**. The low yield of **18** suggested that reduction of the oxime function was a

(8) D. E. O'Brien, C. C. Cheng, and W. Pfleiderer, *J. Med. Chem.*, **9**, 573 (1966).

(9) Alkaline aerobic treatment of related compounds resulted in cleavage at the 9,10 bond and hydrolysis of the 4-amino group; see ref 4.

competing reaction. Oxidation of **18** with $KMnO_4$ gave the heteroaromatic pteridine **22**, and careful hydrolysis of the ester function of the latter with NaOH in DMSO gave the benzoic acid **23**. Although this sample was shown to be homogeneous by its chromatographic behavior and its pmr spectrum, analysis for chlorine showed that this material was a partial hydrochloride.[10] The stability of the 9,10 bond in the 10-N-methyl compound to alkaline conditions has been noted previously.[4]

Experimental Section

Melting points were determined on a Kofler Heizbank or when indicated 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 in deuterated DMSO 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. Thin layer chromatograms were prepared from silica gel H (Brinkmann) and were usually developed with mixtures of $CHCl_3$ and MeOH.

Ethyl *p*-[(3-Aminoacetonyl)amino]benzoate Oxime (5).—A stirred solution of **7** (10.8 g, 28.3 mmol) in EtOH (425 ml) at 70° was treated dropwise under N_2 with 95% NH_2NH_2 (0.98 ml, ~29 mmol). The solution was cooled to 43° and maintained at this temperature for 16 hr. The resulting mixture was refluxed for 30 min, cooled to 25°, and treated dropwise with 1 *N* HCl (28.3 ml, 28.3 mmol). After stirring for 1 hr the mixture was cooled to 0° and filtered to remove phthalhydrazide. The filtrate was evaporated to dryness *in vacuo* at ~40°, the residue was stirred with H_2O (44 ml), and the evaporation was repeated. A solution of the residue in warm H_2O (71 ml) was filtered, cooled to 25°, and treated with charcoal. The resulting filtrate was cooled in an ice bath and treated dropwise with concentrated NH_4OH (1.8 ml) to give a gummy precipitate, which crystallized to a homogeneous powder on stirring. The light tan product was collected by filtration, washed with cold H_2O, and dried *in vacuo* over P_2O_5: yield 5.09 g (72%); mp 122–124°. Tlc showed that this product was a mixture of the *syn*- and *anti*-oxime isomers: λ_{max} nm ($\epsilon \times 10^{-3}$), pH 7, 223 (8.88), 300 (23.2); $\bar{\nu}_{max}$, cm^{-1}, 3410 3360, 3310, 3160 (NH, OH), 1683 (C=O), 1605 (NH), 1595, 1525 (C=C), 1280 (COC).

Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.35; H, 6.82; N, 16.72. Found: C, 57.33; H, 7.01; N, 16.86.

Methyl *p*-[(3-Aminoacetonyl)methylamino]benzoate Oxime (6).—Similarly, a solution of **8** (23.7 g, 62.4 mmol) in EtOH (950 ml) at 50° was treated dropwise with 95% N_2H_4 (2.2 ml, ~64 mmol) and stirred at 39° for 16 hr: yield 11.3 g (71%); mp ~141°. Tlc showed that this product was a mixture of the *syn*- and *anti*-oxime isomers: λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 226 (7.88), 309 (25.7); $\bar{\nu}_{max}$, cm^{-1}, 3360, 3295, 3170 (NH), 3040, 2940, 2830 (CH), 1672 (C=O), 1600, 1575, 1520 (C=C), 1283 (COC).

Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.35; H, 6.82; N, 16.72. Found: C, 57.19; H, 6.63; N, 16.53.

Ethyl *p*-[(3-Phthalimidoacetonyl)amino]benzoate Oxime (7).—A solution of **9** (7.87 g, 21.5 mmol), hydroxylamine hydrochloride (2.24 g, 32.2 mmol), pyridine (20 ml), and EtOH (20 ml) was refluxed under N_2 for 2 hr. The resulting mixture was evaporated to a viscous syrup under reduced pressure (1 mm) at 60°. The syrup was triturated with water (two × 10-ml portions) at 0° and stirred with EtOH (25 ml) until a homogeneous suspension was formed. The mixture was cooled to 15° and the product was collected by filtration, washed with cold EtOH, and dried *in vacuo* over P_2O_5: yield 3.55 g (43%); mp 186°. Tlc showed that the product was a mixture of the *syn*- and *anti*-oxime isomers: λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 222 (10.0), 304 (21.1); $\bar{\nu}_{max}$, cm^{-1}, 3460, 3375 (NH), 2980, 2950, 2935, 2900 (CH), 1760, 1695, 1670 (C=O), 1595, 1570, 1530 (C=C), 1275 (COC).

Anal. Calcd for $C_{20}H_{19}N_3O_5$: C, 62.98; H, 5.02; N, 11.02. Found: C, 63.11; H, 5.09; N, 11.18.

(10) This material was previously reported as the dihydrate; see ref 4.

Methyl *p*-[Methyl(3-phthalimidoacetonyl)amino]benzoate Oxime (8).—Similarly, a solution of **10** (34.8 g, 95.1 mmol), hydroxylamine hydrochloride (9.92 g, 143 mmol), EtOH (85 ml), and pyridine (85 ml) gave a pale yellow crystalline product, which was collected by filtration, washed with cold EtOH, and dried *in vacuo* at 78° over P_2O_5: yield 25.7 g; mp 131°. Tlc showed that this material was a mixture of the *syn*- and *anti*-oxime isomers: λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 314 (22.1); $\bar{\nu}_{max}$, cm^{-1}, 2950, 2900, 2830 (CH), 1765, 1710, 1700 (C=O), 1600, 1550, 1520 (C=C), 1280 (COC).

Anal. Calcd for $C_{20}H_{19}N_3O_5$: C, 62.98; H, 5.02; N, 11.02. Found: C, 62.92; H, 4.93; N, 10.98.

The mother liquor deposited additional product (0.40 g), which was shown by tlc to be a single isomer, mp 148°. The total yield was 26.1 g (72%).

Ethyl *p*-[(3-Phthalimidoacetonyl)amino]benzoate (9).—A mixture of **4** (4.00 g, 14.2 mmol), ethyl *p*-aminobenzoate (2.34 g, 14.2 mmol), $NaHCO_3$ (1.19 g, 14.2 mmol), and anhydrous DMF (50 ml) was stirred at 54° for 16 hr. The resulting solution was filtered and treated dropwise with H_2O (200 ml) at 0°. The pale yellow precipitate was collected by filtration, washed with cold H_2O, and dried *in vacuo* over P_2O_5: yield 3.72 g (72%); mp 216°; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 222 (16.0), 247 (sh), 295 (10.7); $\bar{\nu}_{max}$, cm^{-1}, 3440, 3380 (NH), 2965, 2920, 2880 (CH), 1775, 1725, 1710, 1690 (C=O), 1600, 1520 (C=C), 1270 (COC).

Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.56; H, 4.95; N, 7.65. Found: C, 65.38; H, 4.79; N, 7.82.

Methyl *p*-[Methyl(3-phthalimidoacetonyl)amino]benzoate (10).—Similarly, a mixture of **4** (50.7 g, 180 mmol), methyl *p*-(methylamino)benzoate (29.6 g, 180 mmol), $NaHCO_3$ (15.1 g, 180 mmol), and anhydrous DMF (628 ml) was stirred at 58° for 16 hr. After cooling to 25°, the mixture was filtered (charcoal), and the filtrate was treated dropwise with H_2O (718 ml). The resulting mixture was cooled to 20°, and the product was collected by filtration, washed with 1:1 DMF–H_2O (25 ml) followed by H_2O, and dried *in vacuo* over P_2O_5: yield 22.4 g (34%); mp 195°; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 308 (24.0); $\bar{\nu}_{max}$, cm^{-1}, 3020, 2995, 2945, 2825 (CH), 1773, 1713, 1690 (C=O), 1600, 1555, 1518 (C=C), 1282 (COC).

Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.56; H, 4.95; N, 7.65. Found: C, 65.60; H, 5.00; N, 7.58.

Methyl *p*-({3-[(2,6-Diamino-5-nitro-4-pyrimidinyl)amino]acetonyl}methylamino)benzoate Oxime (13).—Finely powdered **11** (6.04 g, 31.9 mmol) was added in small portions to a stirred suspension of **6** (8.00 g, 31.9 mmol) in EtOH (160 ml). The suspension was treated dropwise with Et_3N (3.02 g, 33.5 mmol) and stirred at 42° for 16 hr. The resulting mixture was cooled to 0°; the product was collected by filtration, washed with cold EtOH, and dried at 78° *in vacuo* over P_2O_5: yield 11.7 g (91%); mp ~140–145° with presoftening from 135° (Mel-Temp); λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 226 (27.6), 317 (30.5); pH 7, 317 (32.8); $\bar{\nu}_{max}$, cm^{-1}, 3460, 3395, 3345, 3190 (NH, OH), 2945, 2910, 2840 (CH), 1695 (C=O), 1605 (NH_2), 1545 (C=C, C=N), 1290 (COC).

Anal. Calcd for $C_{16}H_{20}N_8O_5$: C, 47.52; H, 4.99; N, 27.71. Found: C, 47.29; H, 5.18; N, 27.91.

Ethyl *p*-[3-(2,6-Diamino-5-nitropyrimidin-4-ylamino)acetonylamino]benzoate Hydrochloride (16).—Finely powdered **11** (2.58 g, 13.6 mmol) was added in small portions to a stirred suspension of powdered **5** (3.42 g, 13.6 mmol) in EtOH (68 ml). The suspension was treated dropwise with Et_3N (1.38 g, 13.6 mmol) and stirred at 40° for 17 hr. The resulting mixture was cooled in an ice bath, and the precipitate of **12** was collected by filtration under N_2, washed with cold EtOH, and dried *in vacuo* over P_2O_5: yield 4.71 g (86%); mp 141°. Tlc showed that the product was homogeneous. A portion of the oxime (0.624 g, 1.54 mmol) was added in small portions with stirring to 1 *N* HCl (15.0 ml, 15.0 mmol) at 60°. The mixture was stirred at 60° for 20 min, cooled to 25°, and neutralized by addition of $NaHCO_3$ (1.26 g, 15 mmol). The tan product was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5: yield 0.600 g (92%); mp ~204° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 303 (24.2), 340 (19.5); $\bar{\nu}_{max}$, cm^{-1}, 3380, 3325, 3275, 3230, 3150 (NH), 3050, 2970 (CH), 1728, 1670 (sh) (C=O), 1655 (NH_2), 1600, 1525 (C=C, C=N), 1278 (COC).

Anal. Calcd for $C_{16}H_{19}N_7O_5 \cdot HCl$: C, 45.13; H, 4.73; N, 23.02; Cl, 8.33. Found: C, 45.25; H, 4.53; N, 23.33; Cl, 8.46.

Methyl *p*-({3-[(2,6-Diamino-5-nitro-4-pyrimidinyl)amino]acetonyl}methylamino)benzoate (17).—A stirred solution of **13** (404

mg, 1.00 mmol) in DMAC (10 ml) at 62° was treated dropwise with 1 *N* HCl (10 ml). The resulting mixture was stirred at 62° for 20 min, cooled to 25°, and treated with $NaHCO_3$ (756 mg, 9.00 mmol). The yellow product was collected, washed with H_2O, and dried at 65° *in vacuo* over P_2O_5: yield 290 mg (75%). This sample undergoes slow decomposition above 200°: λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 313 (29.8); $\bar{\nu}_{max}$, cm^{-1}, 3477, 3385, 3350, 3320, 3120 (NH), 2948, 2916, 2900, 2828 (CH), 1719, 1688 (C=O), 1647 (NH_2), 1603, 1551, 1520 (C=C, C=N), 1295 (COC).

Anal. Calcd for $C_{16}H_{19}N_7O_5$: C, 49.36; H, 4.92; N, 25.18. Found: C, 49.16; H, 4.64; N, 25.45.

Methyl *p*-{[(2,4-Diamino-7,8-dihydro-6-pteridinyl)methyl]methylamino}benzoate (18). A.—A suspension of **13** (4.04 g, 10.0 mmol) and EtOH (1 l.) was hydrogenated in the presence of Raney nickel (24 g, weighed wet with EtOH). After 21 hr 995 ml (40 mmol) of H_2 was absorbed. The suspended product was decanted from the catalyst under N_2 and additional product was obtained by rinsing the catalyst with boiling EtOH (five 100-ml portions). The combined EtOH wash was heated to boiling to dissolve most of the solid. After filtration through Celite, the resulting blue solution was treated with charcoal at 25°, filtered through Celite, and evaporated to dryness *in vacuo* to give crude **18** containing **22** (tlc): yield 2.54 g (74%). A portion of the crude product (254 mg) was dissolved in boiling EtOH (80 ml), and the solution was filtered hot through a 2-cm layer of silica gel H covered with Celite in a 3.6-cm-diameter sintered disk funnel. The product was eluted with hot EtOH. The first 70 ml of eluent was discarded and the next 130 ml was refrigerated. Pure **18** separated as yellow crystals, which were collected and dried at 100° *in vacuo* over P_2O_5: yield 54 mg (16%); mp ~275° dec with darkening from ~255° (Mel-Temp); λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 232 (30.2), 294 (26.0), 310 (26.1); pH 7, 294 (sh) (25.6), 313 (29.1); $\bar{\nu}_{max}$, cm^{-1}, 3450, 3370, 3130 (NH), 2940, 2890 (CH), 1693 (C=O), 1600 (NH_2), 1590 (sh), 1523 (C=C, C=N), 1285 (COC); pmr (2.5% w/v), δ 3.04 (3, NCH_3), 3.75 (3, OCH_3), 3.92, 4.14 (2, 2, CH_2), 5.55 (4, NH_2), 6.29 (1, NH), 7.27 (q, 4, C_6H_4).

Anal. Calcd for $C_{16}H_{19}N_7O_2$: C, 56.29; H, 5.61; N, 28.72. Found: C, 56.34; H, 5.57; N, 28.90.

B.—A suspension of **17** (100 mg, 0.257 mmol) in EtOH (25 ml) was hydrogenated in the presence of Raney nickel (~400 mg, weighed wet with EtOH) for 5 days at 25° and 1 day at 40°. The mixture was heated to boiling and the suspended product was decanted from the catalyst, which was then extracted with additional hot EtOH (10 ml). The suspension in EtOH was heated to boiling with charcoal, filtered through Celite, and evaporated to dryness *in vacuo*. Trituration of the residue with EtOH (1 ml) gave a pale yellow solid which was collected, washed with EtOH, and dried *in vacuo* over P_2O_5: yield 34 mg (39%); mp ~275° dec with darkening from ~252° (Mel-Temp). Comparison of the tlc and the ultraviolet, infrared, and pmr spectra of this sample with that prepared above showed that the two samples were identical.

Ethyl *p*-{[(2,4-Diamino-7,8-dihydro-6-pteridinyl)methyl]amino}benzoate (19).—A suspension of finely powdered **16** (3.62 g, 8.50 mmol) and $NaOAc \cdot 3H_2O$ (1.16 g, 8.50 mmol) in EtOH (2 l.) was stirred for 30 min under N_2, then hydrogenated at atmospheric pressure for 2 days in the presence of Raney nickel (20 g, weighed wet with EtOH). Several times during the hydrogenation, the mixture was heated in a water bath at 50°. The supernatant containing suspended product was decanted from the catalyst. The resulting residue was extracted repeatedly with portions of boiling EtOH under N_2 until no solid deposited from the extract. The combined extracts containing suspended product was evaporated to dryness *in vacuo;* the residue was dissolved in DMAC (100 ml) at 100° under N_2, filtered under N_2, and treated dropwise at 0° with H_2O (300 ml). The resulting mixture was refrigerated for 16 hr, and the product was collected by filtration, washed with cold H_2O, and dried at 78° *in vacuo* over P_2O_5: yield 1.60 g (55%); mp ~250° dec with darkening from 220° (Mel-Temp). Tlc indicated that this product contained a trace amount of **20**: λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 231 (27.6), 293 (27.6); pH 7, 294 (27.4); 0.1 *N* NaOH, 294 (26.6); $\bar{\nu}_{max}$, cm^{-1}, 3390 (broad, NH), 2980 (CH), 1680 (C=O), 1600, 1523 (C=C, C=N), 1275 (COC); pmr (10% w/v), δ 1.27 (t, 3, CH_3), 4.07 (m, 6, CH_2), 5.62, 6.05 (4, NH_2), 6.38 (1, NH), 7.22 (q, 4, C_6H_4).

Anal. Calcd for $C_{16}H_{19}N_7O_2$: C, 56.29; H, 5.61; N, 28.72. Found: C, 56.03; H, 5.63; N, 28.52.

Ethyl *p*-{[(2,4-Diamino-6-pteridinyl)methyl]amino}benzoate (20).—A suspension of **19** (3.00 g, 8.80 mmol) in DMAC (88 ml) was stirred for 10 min and treated over a period of 10 min with a 0.27% solution of $KMnO_4$ in Me_2CO (326 ml, 5.57 mmol). The resulting mixture was stirred with $MgSO_4$ (18 g) for 30 sec and filtered rapidly on two 10-cm sintered disk funnels. The precipitate was washed well with Me_2CO and dried *in vacuo* over P_2O_5. This brown powder was stirred with DMSO (88 ml) in a 60° H_2O bath for 2 min and filtered under N_2, and the residue was rinsed with additional DMSO (88 ml). The filtrate was treated with H_2O (352 ml) and refrigerated for 1 hr. The yellow product was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5: yield 1.84 g (62%); mp ~264° dec (Mel-Temp); λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 242 (17.5), 298 (25.2), 335 (sh) (12.6); pH 7, 259 (24.5), 298 (26.1), 372 (8.88); $\bar{\nu}_{max}$, cm^{-1}, 3460, 3310, 3150 (NH), 2977 (CH), 1690 (C=O), 1605, 1525 (NH_2, C=C, C=N), 1275 (COC); pmr (4% w/v), δ 1.27 (t, 3, CH_3), 4.22 (q, 2, OCH_2), 4.51 (d, 2, NCH_2), 6.5, 7.0 (broad, NH), 7.24 (q, C_6H_4), 8.71 (1, ring CH).

Anal. Calcd for $C_{16}H_{17}N_7O_2$: C, 56.63; H, 5.05; N, 28.89. Found: C, 56.58; H, 5.01; N, 28.62.

Methyl *p*-{[(2,4-Diamino-6-pteridinyl)methyl]methylamino}benzoate (22).—A solution of crude **18** (341 mg, 1.00 mmol) in DMAC (10 ml) was treated dropwise with a 0.27% solution of $KMnO_4$ in Me_2CO until the color of permanganate persisted (~16 ml). The resulting mixture was stirred with $MgSO_4$ (2.0 g) for 30 sec and filtered under N_2. The residue was washed well with Me_2CO and dried *in vacuo* over P_2O_5. This solid was stirred with DMSO (10 ml) at 60° for 1 min; the residue was removed by filtration and washed with additional DMSO (10 ml). The combined DMSO extract was treated with H_2O (40 ml) and refrigerated for 1 hr. The crude red product was collected by filtration, washed with H_2O, dried *in vacuo*, and extracted in refluxing EtOH (150 ml) under N_2 for 45 min. The hot extract was filtered through a 3-mm layer of silica gel H covered with Celite in a 3.6-cm-diameter sintered disk funnel. The filtrate was concentrated by boiling to 20 ml and cooled to 25°. The orange product was collected, washed with EtOH, and dried *in vacuo* over P_2O_5: yield 122 mg (36%); mp ~277° dec (Mel-Temp); λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 240 (18.0), 311 (27.9), 350 (sh) (10.4); pH 7, 258 (22.8), 312 (27.1), 373 (8.18); $\bar{\nu}_{max}$, cm^{-1}, 3450, 3300, 3235, 3200, 3100 (NH), 2940, 2830 (CH), 1712 (C=O), 1670, 1630 (NH_2), 1600, 1565, 1520 (C=C, C=N), 1277 (COC); pmr (<10% w/v), δ 3.21 (NCH_3), 3.73 (3, OCH_3), 4.77 (2, CH_2), 6.53, 7.42 (broad, NH_2), 7.28 (q, C_6H_4), 8.58 (1, ring CH).

Anal. Calcd for $C_{16}H_{17}N_7O_2$: C, 56.63; H, 5.05; N, 28.89. Found: C, 56.47; H, 4.98; N, 29.08.

***p*-{[(2,4-Diamino-6-pteridinyl)methyl]methylamino}benzoic Acid (23).**—A solution of **22** (100 mg, 0.295 mmol) in DMSO (6 ml) was treated dropwise with 1 *N* NaOH (0.443 ml, 0.443 mmol), stirred at room temperature for 24 hr, and evaporated to dryness at 50° (0.15 mm) *in vacuo*. The residue was stirred with H_2O (3 ml) for 3 min and filtered under N_2. The remaining solid was washed with H_2O (0.5 ml), and the combined filtrate and wash was adjusted to pH 10 with 1 *N* HCl. The solution was filtered under N_2 and carefully adjusted to pH 7.5 with 1 *N* NaOH. The orange precipitate was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5: yield 54 mg (52%); mp <300°; λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 HCl, 240 (17.3), 311 (24.8), 350 (sh), (9.77); pH 7, 258 (24.6), 285 (22.1), 372 (7.70); 0.1 *N* NaOH, 258 (24.8), 285 (22.1), 372 (7.70); $\bar{\nu}_{max}$, cm^{-1}, 3440, 3380, 3320, 3180 (NH), 2940, 2910 (CH), 1600, 1560, 1525 (NH_2, C=C, C=N); pmr (4% w/v), δ 3.23 (3, NCH_3), 4.82 (2, CH_2), 6.63, 7.51 (NH_2), 7.33 (q, C_6H_4), 8.63 (1, ring CH).

Anal. Calcd for $C_{15}H_{15}N_7O_2 \cdot 0.65HCl$: C, 51.62; H, 4.52; Cl, 6.60; N, 28.09. Found: C, 51.34; H, 4.40; Cl, 6.83; N, 28.35.

Registry No. **5,** 23852-97-3; **6,** 23852-98-4; *syn*-**7,** 23852-99-5; *anti*-**7,** 23890-39-3; *syn*-**8,** 23853-00-1; *anti*-**8,** 23853-01-2; **9,** 23853-02-3; **10,** 23853-03-4; **13,** 23853-04-5; **16**·HCl, 23853-05-6; **17,** 23853-06-7; **18,** 23890-40-6; **19,** 23853-07-8; **20,** 23853-08-9; **22,** 23853-09-0; **23,** 19741-14-1.

Acknowledgments.—The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute who performed most of the microanalytical and spectral determinations reported.

Esters and Amides of 5-Amino-2-aryl-4-pyrimidinecarboxylic Acid

DONG HAN KIM AND ARTHUR A. SANTILLI

Research Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania 19087

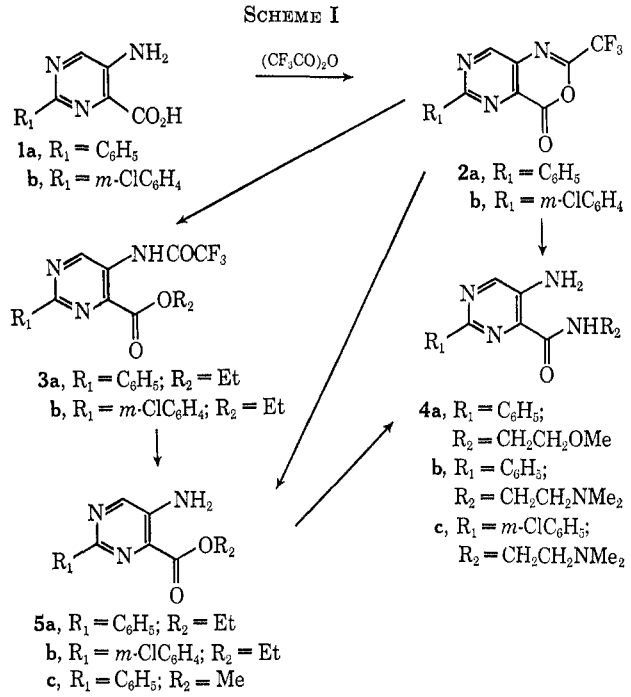
Received October 31, 1969

Although 5-amino-2-phenyl-4-pyrimidinecarboxylic acid (**1**)[1] has been known since 1902, surprisingly, none of its esters or amides has been reported thus far. A review of the literature, furthermore, revealed that neither esters nor amides of 5-amino-4-pyrimidinecarboxylic acids, in general, have been described. The importance of esters and amides of *o*-aminocarboxylic acids as synthetic intermediates for the construction of other heterocycles fused to the original nucleus has been widely recognized for many years.[2]

An application of the conventional Fischer esterification method to **1b** caused extensive decarboxylation, resulting in the formation of 5-amino-2-(*m*-chlorophenyl)pyrimidine. Price, *et al.*,[3] obtained 4-amino-2-methyl-5-pyrimidinecarboxylic acid methyl ester by adding a mixture of methanol and sulfuric acid to a warm solution of the corresponding carboxylic acid in sulfuric acid. An attempt to esterify **1b** by the Price method, however, caused the pyrimidine to suffer the same decarboxylation experienced with the Fischer method. Apparently, decarboxylation of these 5-amino-4-pyrimidinecarboxylic acids occurs with such facility that it presents a major problem in preparing derivatives.

We now wish to report a convenient two-step synthesis of esters and amides of 5-amino-4-pyrimidinecarboxylic acids (see Scheme I). Treatment of **1a,b** with trifluoroacetic anhydride produced in excellent yield the pyrimido[5,4-*d*][1,3]oxazines **2a,b**, the first examples of a previously undescribed heterocyclic ring system. The structures of **2a,b** were supported by elemental analyses and spectral data; their infrared carbonyl absorption bands were exhibited at 5.5 μ. When the intermediates **2a,b** were treated with an appropriate alcohol in the presence of a catalytic amount of base and HCl gas was then introduced, the desired esters **5a–c** were obtained. The products exhibited their ester carbonyl absorption bands at 5.85–5.95 μ. The conversion of **2a,b** into the esters **5a,b** appears to involve a base-catalyzed initial cleavage of the oxazine ring followed by detrifluoroacetylation in the presence of acid. Intermediates **3a,b** were isolated

SCHEME I



when the conversion reaction of **2a,b** into **5a–c** was interrupted prior to the acid treatment. Subsequent treatment of **3a,b** with ethanolic HCl produced **5a** and **5b**. Treatment of **2a** with an excess of 2-methoxyethylamine afforded, in 90% yield, the pyrimidinecarboxamide **4a**, which was identical with the compound obtained from **5a** by refluxing the latter compound with 2-methoxyethylamine. Compounds **4b,c** were prepared similarly by treating **2a,b** with appropriate amines.

Experimental Section

The melting points were taken in capillary tubes (Thomas–Hoover melting point apparatus) and are uncorrected. Infrared spectra were obtained in KBr pellets using a Perkin-Elmer Model 21 spectrophotometer. No effort was made to obtain optimum reaction conditions and yields.

5-Amino-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic acid (1b) was prepared according to the literature method[1] from 5-bromo-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic acid: yield 50%, mp 240–242° dec.

Anal. Calcd for $C_{11}H_8ClN_3O_2$: C, 52.92; H, 3.23; Cl, 14.20; N, 16.83. Found: C, 52.90; H, 3.33; Cl, 14.2; N, 16.77.

5-Bromo-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic acid was prepared from *m*-chlorobenzamidine hydrochloride[4] and mucobromic acid according to the literature method.[5] Recrystallization from 95% EtOH gave a product with mp 162–163° dec.

Anal. Calcd for $C_{11}H_6BrClN_2O_2$: C, 42.14; H, 1.93; N, 8.94; Cl, 11.31. Found: C, 42.36; H, 1.95; N, 8.80; Cl, 11.32.

5-Amino-2-(*m*-chlorophenyl)pyrimidine.—Dry HCl gas was introduced into a mixture of **1b** (1.0 g) and absolute EtOH (70 ml) for 0.5 hr, with occasional cooling, and the resulting mixture was heated on a steam bath for 2 hr. Chilling of the reaction mixture caused separation of a precipitate, which was collected on a filter and treated with 1 *N* aqueous NaOH solution to give a product: mp 154–160° (recrystallization from EtOH–water raised the melting point to 159–161°); ir, no carbonyl absorption band.

Anal. Calcd for $C_{10}H_8ClN_3$: C, 58.40; H, 3.92; N, 20.43; Cl, 17.24. Found: C, 58.67; H, 3.89; N, 20.67; Cl, 17.21.

6-Phenyl-2-trifluoromethyl-4H-pyrimido[5,4-*d*][1,3]oxazin-4-one (2a).—5-Amino-2-phenyl-4-pyrimidinecarboxylic acid (**1a**)

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