New Approaches to the Synthesis of 5H-Pyrrolo[3,2-*d*]pyrimidines[1]

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A new synthetic route to the 5H-pyrrolo[3,2-*d*]pyrimidine ring system *via* the reaction of 4,6-dichloro-5-nitropyrimidine (I) with ketene diethyl acetal has been developed and applied to the synthesis of six examples of this ring system: 6-ethoxy-5H-pyrrolo[3,2-*d*]pyrimidine (VI), 6-ethoxy-5H-pyrrolo[3,2-*d*]pyrimidin-4(3H)-one (IX), ethyl 4-amino-5H-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (XII), 4-amino-5H-pyrrolo[3,2-*d*]pyrimidine-7-carboxylic acid (XV), 4-amino-5H-pyrrolo[3,2-*d*]pyrimidin-6-one (XVI), and 4-amino-5H-pyrrolo[3,2-*d*]-pyrimidine (9-deazaadenine, XX). The ease of ring closure to this heterocyclic system is notable.

Surprisingly few examples of the 5H-pyrrolo[3,2-*d*]-pyrimidine (9-deazapurine) ring system have been reported.[2-4] Two of the syntheses of this ring system are based on the reactivity of the methyl group in the 4-position of pyrimidines. One of these methods involves a Claisen-type condensation of diethyl oxalate with the methyl group to provide an intermediate for ring closure,[2,3] while the other is a ring closure between the carbonyl of an acylamino group in the 5-position of the pyrimidine ring and the methyl group at position 4.[2]

The original 5H-pyrrolo[3,2-*d*]pyrimidine synthesis was based on the reaction of 4-chloro-5-nitropyrimidines with diethyl malonate.[4] Reduction of the nitro group of the resultant 5-nitro-4-pyrimidinemalonic acid diethyl ester gave the intermediate that was cyclized to a pyrrolo[3,2-*d*]pyrimidine. Unfortunately and contrary to the first report,[4] it was later found that the reaction of diethyl malonate with 4-chloro-5-nitropyrimidines unsubstituted in the 2-position takes place in an anomalous fashion to give 5-amino-2-pyrimidinemalonic acid diethyl esters,[5] unsuitable for cyclization to pyrrolo[3,2-*d*]pyrimidines. We have now found that reaction of 4,6-dichloro-5-nitropyrimidine (I) with ketene diethyl acetal[6] in ether proceeded satisfactorily to give 4-chloro-6-(2,2-diethoxyvinyl)-5-nitropyrimidine (II) (see Scheme I). Thus the complication encountered in the reaction of I with the sodio derivative of diethyl malonate[5] and related compounds was avoided. Catalytic reduction of the nitro group of II at atmospheric pressure in the presence of Davidson sponge nickel catalyst was slow; the product, thought to be 5-amino-4-chloro-6-(2,2-diethoxyvinyl)pyrimidine, was isolated and further reduced with palladium-on-charcoal catalyst in an attempt to prepare 5-amino-4-chloro-6-(2,2-diethoxyethyl)pyrimidine. The palladium reduction was stopped when the theoretical amount of hydrogen was consumed, even though there was no change in the rate of hydrogen consumption. Two products were isolated from the reaction mixture. They were identified on the basis of their elemental analyses and ultraviolet, infrared, and proton magnetic resonance spectra (and neutral equivalent in the case of IX) as 6-ethoxy-5H-pyrrolo[3,2-*d*]pyrimidine (VI) and 6-ethoxy-5H-pyrrolo[3,2-*d*]pyrimidin-4(3H)-one (IX). An examination of the ultraviolet and infrared spectra of the product of the first reduction step indicated that cyclization followed formation of the amino group and that the compound actually subjected to the second reduction was probably 4-chloro-6-ethoxyl-5H-pyrrolo[3,2-*d*]pyrimidine (III). The second reduction procedure resulted in hydrogenolysis of the chloro group of III to give VI and hydrolysis of the chloro group of III (during the work-up procedure) to give IX. Since the theoretical amount of hydrogen was consumed and since the yields of VI and IX were low, it seems reasonable to assume that ring reduction also occurred.

The behavior of II on reduction is supported by its behavior on treatment with cold methanolic ammonia. In addition to the expected replacement of the chloro group of II by an amino group, the diethoxyvinyl group was converted to an imino ester group, a reaction for which no precedent is apparent. The resultant compound, ethyl-6-amino-5-nitro-4-pyrimidineacetimidate (IV), on treatment with ethanol containing 1 equiv. of hydrochloric acid, was hydrolyzed to ethyl 6-amino-5-nitro-4-pyrimidineacetate (VII), which was also prepared in another way (see below). Catalytic reduction of IV at atmospheric pressure with palladium-on-charcoal catalyst gave a mixture from which a 50% yield of ethyl 5,6-diamino-4-pyrimidineacetate (VIII) was isolated. Obviously, under the conditions of the reduction, hydrolysis of the imino ester occurred, in all probability prior to reduction.

On standing for about 2 weeks in a vial at room temperature, a sample of 4-chloro-6-(2,2-diethoxyvinyl)-5-nitropyrimidine (II) liquefied. An examination of the infrared spectrum of the liquid showed a strong ester carbonyl band at 1740 cm.$^{-1}$. In other respects the spectrum was similar to that of the vinylpyrimidine II. The presence of this ester band can only be explained as resulting from hydrolysis of the diethoxyvinyl group[7] to give ethyl 6-chloro-5-nitro-4-pyrimidineacetate (V). This compound was also obtained by refluxing a 90% ethanol solution of II for 1 hr. and by allowing II to stand in an ether solution containing 1 equiv. of HCl at room temperature for 1 hr. Ethyl 6-chloro-5-nitro-4-pyrimidineacetate (V), on treatment with cold methanolic ammonia, was converted cleanly to ethyl 6-amino-5-nitro-4-pyrimidineacetate (VII). This route to VII and thus to VIII is more satisfactory than the one described above.

Hydrolysis of the ester group of VIII was attempted by refluxing it in 6 *N* hydrochloric acid. Instead of hydrolysis, ring closure to 4-amino-5H-pyrrolo[3,2-*d*]-pyrimidin-6-one (XVI) occurred, again showing[4] the

(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. PH-43-64-51.

(2) K. Tanaka, T. Sugawa, R. Nakamori, Y. Sanno, and Y. Ando, *J. Pharm. Soc. Japan*, **75**, 770 (1955); K. Tanaka, T. Sugawa, R. Nakamori, Y. Sanno, Y. Ando, and K. Imai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1024 (1964).

(3) W. Pfleiderer and H. Mosthaf, *Chem. Ber.*, **90**, 738 (1957).

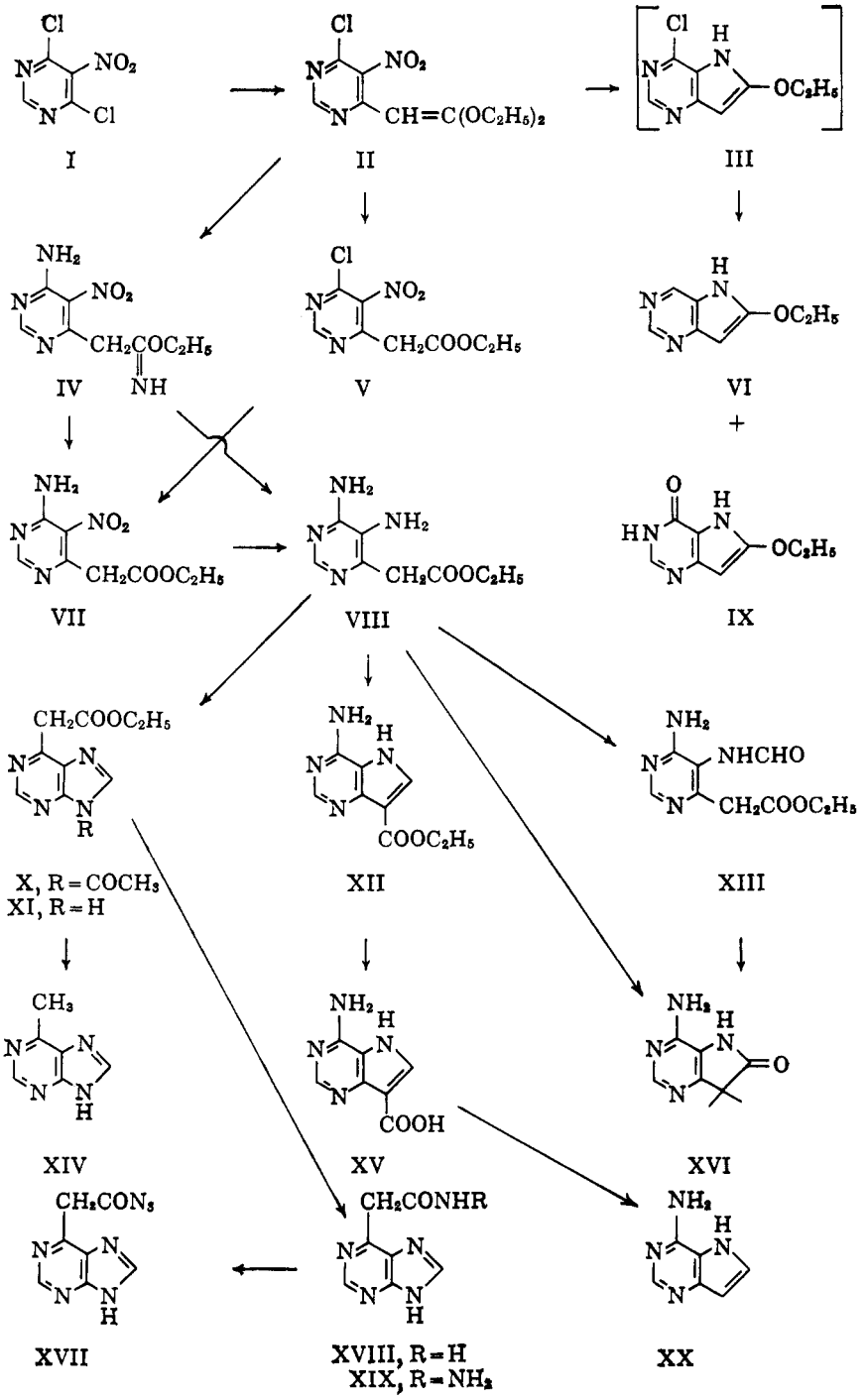
(4) F. L. Rose, *J. Chem. Soc.*, 4116 (1954).

(5) F. L. Rose and D. J. Brown, *ibid.*, 1953 (1956).

(6) The reaction of cyanuric chloride with vinyl acetal has been reported.[7]

(7) E. Kober, *J. Org. Chem.*, **26**, 4705 (1961).

SCHEME I



propensity of the group in 4-position of these pyrimidines to react with the 5-amino group; the reaction was complete in 15 min. The proton magnetic resonance spectrum of XVI showed the presence of the methylene group at position 7 and the infrared spectrum showed a carbonyl group, thus establishing the structure of XVI to be as depicted.

Treatment of VIII with 1 equiv. of phosphorus oxychloride in N,N-dimethylformamide, a reagent pair known to formylate active methylene groups[8] and to cyclize 4,5-diaminopyrimidines to purines with facility,[9] gave a precipitate which was converted on refluxing in 6 *N* hydrochloric acid to a mixture of 6-methylpurine XIV and 4-amino-5H-pyrrolo[3,2-*d*]pyrimidin-6-one (XVI). Treatment of an aqueous solution of the precipitate with Amberlite IR-4B (OH^-) ion-exchange resin gave ethyl purine-6-acetate (XI), identified by comparison with an authentic sample (see below), and an intractable oil. These results indicated to us that the original precipitate was a mixture of the hydrochlorides of XI and ethyl 6-amino-5-formamido-4-pyrimidineacetate (XIII). An analytical sample of ethyl 4-amino-5-formamido-4-pyrimidineacetate (XIII) was prepared for comparison by the reaction of VIII with 98% formic acid. Thus, the acid hydrolysis of the mixture of XI and XIII gave purine 6-acetic acid, which decarboxylated spontaneously to 6-methylpurine (XIV) (see below), and VIII which cyclized in acid to XVI (see above).

(8) F. T. Tyson and J. T. Shaw, *J. Am. Chem. Soc.*, **74**, 2273 (1952).

(9) J. Clark and G. R. Ramage, *J. Chem. Soc.*, 2821 (1958); J. Clark and J. H. Lister, *ibid.*, 5048 (1961).

If VIII was treated with 5 equiv. of phosphorus oxychloride in twice the previously used volume of N,N-dimethylformamide, quite a different result was obtained. Cyclization between the 5-amino group and the methylene group of VIII occurred giving the hydrochloride of ethyl 4-amino-5H-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (XII) and a small amount of ethyl purine-6-acetate. This compound (XII) was identified by its elemental analyses and its infrared and proton magnetic resonance spectra. Hydrolysis of XII to the corresponding acid, 4-amino-5H-pyrrolo[3,2-*d*]pyrimidine-7-carboxylic acid (XV), was accomplished in 6 *N* hydrochloric acid and thermal decarboxylation of XV mixed with powdered glass took place smoothly to give 4-amino-5H-pyrrolo[3,2-*d*]pyrimidine (9-deazaadenine, XX).[10]

The reaction of VIII with diethoxymethyl acetate, another reagent known to react with active methylene groups[12] and to cyclize 4,5-diaminopyrimidines to purines with facility,[13] produced a mixture of ethyl purine-6-acetate (XI) and its N-acetyl derivative (X),[14] which can be converted to XI. This reaction is sensitive to concentration of substrate and to temperature. Under optimum conditions for the formation of X and XI, a significant amount of a side product, which was converted by further treatment with diethoxymethyl acetate followed by acid hydrolysis into 6-methylpurine (XIV), was formed. At higher concentrations of substrate and higher temperatures the product was exclusively this side product that has not been further characterized. Reaction of X or XI with methanolic ammonia at 130° in a bomb and with anhydrous hydrazine at room temperature gave purine 6-acetamide (XVIII) and purine-6-acetic acid hydrazide (XIX), respectively. Treatment of the hydrazide XIX with nitrous acid gave the acid azide XVII, which was characterized by its infrared spectrum and conversion to the corresponding urethan. The azide XVII, however, was so unstable that it could not be purified and decomposed almost completely on dissolving it in water.

Purine 6-acetic acid itself proved surprisingly unstable[16]; all attempts to prepare the sodium salt of the acid by base saponification of XI or the acid by acid hydrolysis of XI resulted in decarboxylation, and only 6-methylpurine (XIV) could be isolated.

Experimental

The melting points reported were determined on a Kofler hot stage and are corrected. The ultraviolet spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer. The infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 221 spectrophotometer. The p.m.r. spectra were determined with a Varian Associates Model A-60 spectrometer; probe temperature was 38 ± 1°; the solvent used was DMSO-d_6 except in the case of XV which, because of its solubility, was run in trifluoroacetic acid.

4-Chloro-6-(2,2-diethoxyvinyl)-5-nitropyrimidine (II).—To a solution of 4,6-dichloro-5-nitropyrimidine (I, 3.2 g., 16.6 mmoles) in anhydrous ether (200 ml.) was added freshly distilled ketene diethyl acetal (19 g.), and the solution was refluxed for 4 hr. The red reaction solution was concentrated *in vacuo* to a thick sirup. The crystals that formed on concentration were collected by filtration, washed with cyclohexane, and dried *in vacuo*. The filtrate and washings were combined and concentrated *in vacuo;* the process was repeated until crystals no longer formed in the residual red oil. The total yield of crude product (2.4 g.) was dissolved in warm cyclohexane, (50–75 ml.) and the solution was filtered through dry Celite to remove a red insoluble material. The yellow filtrate was concentrated under nitrogen to 30 ml. and allowed to stand until crystallization was complete. The purified product was collected, washed with cyclohexane, dried *in vacuo*, and stored protected from light and moisture: 2.14 g. (47%), m.p. 100°.

An analytical sample was prepared from a previous 2-g. run after two recrystallizations from cyclohexane: 597 mg. (21%); m.p. 100°; R_f (water-saturated butanol) 0.89; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 245 (broad) (3.4), at pH 7 327 (21.3), in ethanol 322 (21.2), and at pH 13 270 (8.3) and 320 (broad) (10.7); $\bar{\nu}_{max}$ 3000, 2940 (CH), 1610, 1570, 1530 (C=C, C=N), 1550, 1355 (NO_2), and 1080 (COC) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{12}ClN_3O_4$: C, 44.00; H, 4.45; N, 15.40. Found: C, 44.18; H, 4.44; N, 15.11.

The Reduction of 4-Chloro-6-(2,2-diethoxyvinyl)-5-nitropyrimidine (II).—Davidson sponge nickel catalyst (3 g.) was added to a solution of 4-chloro-6-(2,2-diethoxyvinyl)-5-nitropyrimidine (II, 1.75 g., 6.4 mmoles) in ethanol (200 ml.) and the mixture was hydrogenated at atmospheric pressure. After the theoretical amount of hydrogen (19.2 mmoles) had been consumed (4 hr.), the catalyst was removed by filtration, and the filtrate was collected in a solution of glacial acetic acid (0.5 ml., 8.5 mmoles) in ethanol (20 ml.). Palladium-on-charcoal (5%) catalyst (175 mg.) was added to the filtrate, and the reaction mixture was hydrogenated at atmospheric pressure. After the theoretical amount of hydrogen (12.8 mmoles) had been consumed (4 hr.), the catalyst was removed by filtration and the filtrate was evaporated to dryness. The semisolid residue was triturated with ethanol and the insoluble solid remaining was collected by filtration yielding 475 mg. of crude **6-ethoxy-5H-pyrrolo[3,2-*d*]pyrimidin-4(3H)-one hydrochloride (IX)**. Two recrystallizations of the crude product from ethanol (20 ml., 10 ml.) gave the pure material: 140 mg. (10%); m.p. dec. above 180°; R_f (isopropyl alcohol–ammonium hydroxide–water, 15:1:5) 0.54; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 228 (15.4), 286 (7.2), and 321 (5.3); at pH 7 250 (18.9) and 297 (6.5); and at pH 13 247 (22.2) and 296 (6.6); $\bar{\nu}_{max}$ 3160, 3095, 3010, 2905 (CH), 2780–2560 (acidic H), 1662 (C=O), 1580, 1550, 1530, 1510 (C=C, C=N), and 1020 (COC) cm.$^{-1}$; τ 8.53 (t, CH_3), 5.40 (q, CH_2), 3.52, 0.08 broad (NH, 3 protons), 1.08 and 1.03 (C_2H and C_7H) p.p.m.

Anal. Calcd. for $C_8H_{10}ClN_3O_2$: C, 44.55; H, 4.68; Cl, 16.45; N, 19.50; mol. wt., 214.67. Found: C, 44.59; H, 4.99; Cl, 16.3; N, 19.64; mol. wt., 215 (by titration).

All filtrates from the isolation of IX were combined and evaporated to dryness *in vacuo*. The residue was triturated with boiling acetone and the insoluble pigments were removed by filtration. The filtrate was neutralized with ammonium hydroxide and the crude VI was fractionally crystallized from the mixture to give a crude yield of 128 mg. Recrystallization of the crude product from acetone and then water gave the pure **6-ethoxy-5H-pyrrolo[3,2-*d*]pyrimidine (VI)**: 50 mg. (4.8%); m.p. dec. above 160°; R_f (isopropyl alcohol–ammonium hydroxide–water, 15:1:5) 0.82; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 240 (10.8), 279 (5.3), and 311 (10.1); at pH 7 225 (15.0) and 294 (9.3); and at pH 13 232 (21.8), 290 (6.0), and 305 (sh) (5.0); $\bar{\nu}_{max}$ 3130, 3050, 2980 (CH), 2810–2600 (acidic H), 1630, 1560, 1545 (C=C, C=N), 1195 and 1040 (COC) cm.$^{-1}$.

Anal. Calcd. for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.53; H, 5.44; N, 25.70.

Ethyl 6-Amino-5-nitro-4-pyrimidineacetimidate (IV).—Absolute methanol (175 ml.) was saturated at 5° with dry ammonia.

(10) After this manuscript had been accepted for publication, a report[11] of the synthesis of this compound by another method was brought to the attention of the authors.

(11) K. Imai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1030 (1964).

(12) H. W. Post and E. R. Erickson, *J. Org. Chem.*, **2**, 260 (1937).

(13) J. A. Montgomery and L. B. Holum, *J. Am. Chem. Soc.*, **80**, 404 (1958).

(14) Although we have represented this compound as the 9-acetyl derivative we have made no effort to establish the true position of the acetyl group. N-Acetyl-6-methylpurine, prepared by the acetylation of 6-methylpurine with acetic anhydride, has been shown to be the 9 isomer, although the acetylation of purine gives a 1:1 mixture of the 7 and the 9 isomers.[15]

(15) G. S. Reddy, L. Mandell, and J. H. Goldstein, *J. Chem. Soc.*, 1414 (1963).

(16) Purine 6-carboxylic acid[17] and purine-6-propionic acid[18] are stable compounds. Furthermore uracil-6-acetic acid is prepared by the reaction of acetonedicarboxylic acid with urea in fuming sulfuric acid.[19]

(17) L. B. Mackay and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3571 (1956).

(18) H. Lettre and C. Woenckhaus, *Ann.*, **649**, 131 (1961).

(19) G. E. Hilbert, *J. Am. Chem. Soc.*, **54**, 2076 (1932).

4-Chloro-6-(2,2-diethoxyvinyl)-5-nitropyrimidine (II, 3 g., 11 mmoles) was dissolved in the cold ammonia solution and the resulting dark red reaction solution was allowed to stand in the refrigerator overnight. The orange crystals that precipitated on standing were collected by filtration, washed with fresh methanol, and dried *in vacuo* to give the crude product in a 70% yield. An additional 8% of crude product was obtained on concentration of the combined filtrate and washings to one-fourth volume. The total crude product was triturated with ether before it was recrystallized from a minimum of boiling ethanol. After chilling the solution for several hours, the pure product was collected by filtration, washed with fresh ethanol, and dried *in vacuo:* 1.6 g. (63%), m.p. 200°.

The analytical sample was prepared from a previous small-scale run and was isolated from the reaction mixture in 69% yield: m.p. 197°; R_f (water-saturated butanol) 0.81; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 217 (15.7), 247 (sh), 253 (5.4), 258 (sh), 296 (5.8), 324 (5.1), 330 (sh); at pH 7 216 (16.0), 302 (15.4), and 340 (broad) (3.9); and at pH 13 230 (12.3), 294 (15.4), and 340 (sh); $\bar{\nu}_{max}$ 3430, 3410, 3380, 3360, 3300 (NH), 3110, 2990, 2940 (CH), 1620 (NH), 1550, 1500 (C=C, C=N), 1530, 1340 (NO_2), 1240 and 1050 (COC) cm.$^{-1}$.

Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.70; H, 4.93; N, 31.13. Found: C, 42.82; H, 4.79; N, 31.29.

Ethyl 6-Amino-5-nitro-4-pyrimidineacetate (VII).—A mixture of 4-chloro-6-(2,2-diethoxyvinyl)-5-nitropyrimidine (II; 2.75 g., 10 mmoles) in ethanol (40 ml.) was stirred for 2 hr. before 1 ml. of water was added and the resulting mixture was stirred at room temperature overnight. The clear solution was evaporated to dryness *in vacuo* and the residue was dissolved in 15 ml. of methanol saturated with ammonia at 5°. This solution was stoppered and stored in the refrigerator overnight. The crystals that formed in the reaction mixture were collected by filtration, washed with methanol, and air dried to give 1.76 g. (78%) of crude product; m.p. 182°. The crude product was triturated successively with boiling ethanol (100 ml.), boiling chloroform (50 ml.), and boiling water (40 ml.). After each trituration, the mixture was cooled to room temperature and the insoluble solid was collected by filtration and air dried before it was triturated in the next solvent of the series. Finally the water-insoluble solid was dried *in vacuo* at 78°: 1.2 g. (54%); m.p. 226°; R_f (water-saturated butanol) 0.74; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 217 (15.8), 252 (7.5), and 330 (broad) (3.1); at pH 7 217 (18.8), 250 (4.8), 285 (2.1), and 345 (broad) (4.0); and at pH 13 230 (sh), 295 (14.4), and 332 (broad; 5.6); $\bar{\nu}_{max}$ 3380, 3360, 3280 (NH), 3080 broad (OH, CH), 1715 (C=O), 1620 (NH), 1590, 1550 (C=C, C=N), and 1175 (COC) cm.$^{-1}$.

Anal. Calcd. for $C_8H_{10}N_4O_4$: C, 42.51; H, 4.46; N, 24.79. Found: C, 42.43; H, 4.34; N, 24.80.

Ethyl 5,6-Diamino-4-pyrimidineacetate (VIII). A.—Ethyl 6-amino-5-nitro-4-pyrimidineacetimidate (IV, 1.13 g., 5 mmoles) was suspended in ethanol (400 ml.) and the mixture was hydrogenated at atmospheric pressure in the presence of 5% palladium-on-charcoal catalyst (120 mg.). The reaction mixture consumed the theoretical amount of hydrogen in 8 to 10 hr. to give a pale yellow reaction solution. The catalyst was removed by filtration through dry Celite and the filtrate was evaporated to dryness. The resulting residue was triturated in boiling benzene (300 ml.) for a few minutes before it was filtered to remove the insolubles. The filtrate was allowed to stand until crystallization was complete. The purified product was collected in several crops to give a total yield of 355 mg. (48%) of chromatographically homogeneous material contaminated with a small amount of pigmented material. The pure product was obtained by recrystallization from benzene: 235 mg. (32%); m.p. 156°; R_f (water-saturated butanol) 0.67; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 294 (9.7), at pH 7 249 (6.0) and 290 (7.1), and at pH 13 245 (6.5) and 290 (6.9); $\bar{\nu}_{max}$ 3420, 3300, 3130 (NH), 2960, 2900 (CH), 1715 (C=O), 1655 (NH), 1580, 1490 (C=C, C=N), and 1230 (COC) cm.$^{-1}$.

Anal. Calcd. for $C_8H_{12}N_4O_2$: C, 49.53; H, 6.24; N, 28.88. Found: C, 49.51; H, 6.31; N, 28.82.

B.—Ethyl 6-amino-5-nitro-4-pyrimidineacetate (VII, 1.13 g., 5.05 mmoles) was suspended in 350 ml. of absolute ethanol. Palladium-on-charcoal (5%) catalyst (100 mg.) was added and the mixture was hydrogenated at atmospheric pressure. Complete hydrogenation required 18 to 20 hr. The catalyst was removed by filtration through dry Celite and the filtrate was evaporated to dryness. Trituration of the residue with ether containing a little ethanol gave the crude product which was collected by filtration and dried *in vacuo:* 880 mg. (85%), m.p. 150°. Pure product can be obtained by recrystallization of the crude product from benzene as described above.

Ethyl Purine-6-acetate (XI).—A mixture of ethyl 5,6-diamino-4-pyrimidineacetate (VII, 500 mg., 2.6 mmoles) in diethoxymethylacetate (25 ml.) was stirred until solution was complete (10 min.). After standing at room temperature overnight, the reaction solution was evaporated to dryness *in vacuo* (5 mm., 40°). Volatiles were removed from the residue by evaporation *in vacuo* with additions of ethanol leaving a crude oil which was then dissolved in ether (8 ml.). The ether solution was treated with Norit and filtered; the filtrate was allowed to stand in the refrigerator until crystallization was complete. The crystals were collected by filtration and identified by the infrared spectrum as ethyl N-acetylpurine-6-acetate (X): 253 mg. (40%); m.p. 95°; thin layer chromatography on silica gel H (Merck) using chloroform–methanol (95:5) as the eluent showed a single spot; $\bar{\nu}_{max}$ 3095, 2985, 2930 (CH), 1755, 1735 (C=O), 1590, 1575, 1490 (C=C, C=N), and 1160 (COC) cm.$^{-1}$.

The N-acetylpurine was dissolved in water (8 ml.) and the solution was boiled for 2 min. before it was evaporated to dryness *in vacuo*. The resulting residue was dissolved in benzene and the solution was allowed to stand until crystallization was complete. The pure ethyl purine-6-acetate was collected by filtration in two crops: total yield 124 mg. (23%); m.p. 135°; thin layer chromatography on silica gel H (Merck) using chloroform–methanol (95:5) as the eluent showed a single spot; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 263 (8.0), at pH 7 247 (sh) and 264 (9.1), and at pH 13 273 (9.3); $\bar{\nu}_{max}$ 3120, 3080, 2980, 2930 (CH), 2800–2500 (acidic H), 1725 (C=O), 1615 (C=C, C=N), 1190 (COC) cm.$^{-1}$.

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.44; H, 4.89; N, 27.17. Found: C, 52.67; H, 4.87; N, 27.32.

The Hydrolysis of Ethyl Purine-6-acetate (XI). A. In Acid.—A solution of ethyl purine-6-acetate (100 mg., 0.5 mmole) in 0.1 *N* hydrochloric acid (5 ml.) was refluxed for 4 hr. The reaction solution was evaporated to dryness *in vacuo* and the residue was crystallized from a mixture of ethanol and ether: 43 mg. (51%); sublimes above 190°; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 263 (6.8), at pH 7 245 (sh) and 261 (7.8), and at pH 13 271 (8.2); $\bar{\nu}_{max}$ 3510, 3400, 3250, 3040, 2980, 2900, 2800–2500 (CH and acidic H), 1650, 1600 (C=C, C=N), 1480 (CH), 920 and 880 (purine ring) cm.$^{-1}$. This spectrum was identical with that of 6-methylpurine hydrochloride prepared from an authentic sample of 6-methylpurine.

B. In Base.—A solution of ethyl purine-6-acetate (100 mg., 0.5 mmole) in 0.1 *N* sodium hydroxide (5 ml.) was allowed to stand at room temperature. The reaction was followed by thin layer chromatography on silica gel H (Merck) using chloroform–methanol as eluent (9:1). After 24 days only a small amount of starting compound could be detected. The reaction was worked up by adjusting the pH of the solution to pH 5 (pH of distilled water) with Rexyn RG 50 (H) ion-exchange resin. The neutral solution was evaporated to dryness *in vacuo* and the oily residue was identified by its infrared and ultraviolet spectra as impure 6-methylpurine.

4-Amino-5H-pyrrolo[3,2-*d*]pyrimidine-7-carboxylic Acid Ethyl Ester (XII) Hydrochloride.—Phosphorus oxychloride (10 ml., 110 mmoles) was added dropwise to a stirred solution of ethyl 5,6-diamino-4-pyrimidinyl acetate (4 g., 21 mmoles) in anhydrous N,N-dimethylformamide (200 ml.). The resulting reaction solution was allowed to stand at room temperature overnight before it was evaporated to dryness *in vacuo*. The oily residue was diluted with water (50 ml.) with continuous stirring and cooling to keep the mixture from boiling. The solid that precipitated on cooling was collected by filtration, washed with water, ethanol, and ether, and dried *in vacuo:* 4 g. (80%); m.p. 274°; $\bar{\nu}_{max}$ 3340, 3240 (NH), 3080 (NH_3^+), 2860 (CH), 2800–2600 (acidic H), 1720 (ester C=O), 1670, 1620, 1590 (NH, C=C, C=N), 1460 (CH), and 1170 (COC) cm.$^{-1}$; τ 0.55 (N–4 H, 2 protons), 1.48 and 1.57 (C_2H and C_6H), 5.62 (q, CH_2), 8.65 (t, CH_3) p.p.m. Thin layer chromatography on silica gel H (Merck) using chloroform–methanol (3:1) as the eluent indicated that the product was homogeneous and suitable for use as an intermediate.

The analytical sample of the free base XII was obtained from a preliminary run using 388 mg. (2 mmoles) of VII. Trituration of the crude hydrochloride with dilute ammonium hydroxide followed by recrystallization from 50 ml. of aqueous ethanol gave the pure product: 133 mg. (32%); m.p. dec. above 300°; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 234 (29.8) and 270 (15.6), at pH 7 233 (38.0) and 277 (broad) (10.2), and at pH 13 248 (44.2) and 294

(6.6); $\bar{\nu}_{max}$ 3480, 3390, 3350, 3220, 2980 (NH and CH), 1700 (sh), 1680, 1645, 1605, 1555 (C=O, NH, C=C, C=N), 1450 (CH), 1240 and 1150 (COC) cm.$^{-1}$.

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.44; H, 4.89; N, 27.17. Found: C, 52.53; H, 4.93; N, 27.25.

Ethyl 6-Amino-5-formamido-4-pyrimidinylacetate (XIII).—A solution of ethyl 5,6-diamino-4-pyrimidinylacetate (VIII; 510 mg., 2.6 mmoles) in 98% formic acid (25 ml.) was refluxed for 20 hr. before the solution was evaporated to dryness *in vacuo* and the residue was triturated with ethanol. The ethanol-insoluble material was removed by filtration. The filtrate was treated with Norit and filtered, and the filtrate was concentrated until crystallization was initiated. The pure product was obtained in two crops: 160 mg. (27%); m.p. 173°; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 239 (sh), 251 (11.0), and 265 (sh); at pH 7 233 (13.2) and 276 (4.8); and at pH 13 249 (10.4) and 281 (broad) (6.6); $\bar{\nu}_{max}$ 3325, 3200, 2980, 2940 (NH, CH), 1720 (ester C=O), 1680 (amide C=O),164 0 (NH), 1590, 1550, and 1495 (C=C, C=N) cm.$^{-1}$.

Anal. Calcd. for $C_9H_{12}N_4O_3$: C, 48.25; H, 5.40; N, 25.01. Found: C, 48.33; H, 5.26; N, 25.14.

4-Amino-5H-pyrrolo[3,2-*d*]pyrimidine-7-carboxylic Acid (XV).—A suspension of ethyl 4-amino-5H-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (XII) hydrochloride (1 g., 4.14 mmoles) in 6 *N* hydrochloric acid (50 ml.) was refluxed for 4 hr. Complete solution was obtained at the boiling point and the product began to precipitate within 30 min. The reaction mixture was cooled to room temperature, and the insoluble solid was collected by filtration, washed with water and ethanol, and dried *in vacuo* to give the crude product as the hydrochloride salt: 774 mg. (89%), m.p. 286–288°. The free base was obtained in a 51% yield by crystallization from a neutralized (1 *N* sodium hydroxide) boiling water solution of the salt. The analytical sample was obtained by recrystallizing a sample of the free base from boiling water; this sublimes above 260°. Thin layer chromatography on crystalline cellulose (Avicel) using butanol–acetic acid–water (5:2:3) showed a single spot: λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 233 (27.0), 270 (14.5), and 290 (sh); at pH 7 232 (23.0), 272 (12.8), and 290 (sh); and at pH 13 244 (17.5), 265 (sh), 290 (sh), and 300 (sh); $\bar{\nu}_{max}$ 3390, 3240 (NH), 3040 (NH_3^+), 2900–2600 (CH, acidic H) 1685, 1625, 1600, 1580 (COO^-, NH, C=C, C=N), 1460 (CH), and 1365 (COO^-) cm.$^{-1}$; τ 1.07 and 1.52 (C_2H and C_6H) p.p.m., NH and COOH absorption obscured by exchange with solvent.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.23; H, 3.40; N, 31.48. Found: C, 46.84; H, 3.50; N, 31.08.

4-Amino-5H-pyrrolo[3,2-*d*]pyrimidin-6-one (XVI) Hydrochloride. A.—A solution of ethyl 5,6-diamino-4-pyrimidineacetate (VIII, 250 mg., 1.3 mmoles) in 6 *N* hydrochloric acid (25 ml.) was refluxed for 15 min. The amorphous solid that formed was removed by filtration and the filtrate was concentrated *in vacuo*. The crude product that precipitated on concentration was collected in two crops which were combined and recrystallized from 1 *N* hydrochloric acid to give pure material: 108 mg. (45%); m.p. dec. above 230°; thin layer chromatography on silica gel H (Merck) using chloroform–methanol (1:1) as the eluent showed one spot; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 213 (sh), 240 (8.2), and 286 (10.2); at pH 7 235 (sh), 252 (15.6), and 307 (9.0); and at pH 13 237 (22.0) and 297 (16.1); $\bar{\nu}_{max}$ 3360, 3320, 3130, 3050, 3030 (NH and CH), 2900–2600 (acidic H), 1680 (C=O), 1635 (NH), 1600, 1570, and 1515 (C=C, C=N) cm.$^{-1}$; τ 6.48 (C-7 H, 2 protons), 3.52 (N-4 H, 2 protons), 1.88 (C-2 H), and 0.23 broad (N-5 H) p.p.m.

Anal. Calcd. for $C_6H_7ClN_4O$: C, 38.61; H, 3.78; N, 30.02. Found: C, 38.38; H, 3.80; N, 30.18.

B.—A solution of ethyl 6-amino-5-formamido-4-pyrimidinylacetate (30 mg.) in 6 *N* hydrochloric acid (2 ml.) was heated in a boiling water bath for 5 min. Evaporation of the solution to dryness *in vacuo* gave an oily residue which was identified by its infrared spectrum and thin layer chromatogram [on silica gel H (Merck) using chloroform–methanol (3:1) as the eluent] as 4-amino-5H-pyrrolo[3,2-*d*]pyrimidin-6-one.

Purine-6-acetamide (XVIII).—A solution of ethyl N-acetylpurine-6-acetate (X, 500 mg., 2 mmoles) in dry methanolic ammonia (25 ml.) was heated at 90° in a glass-lined bomb for 5 hr. After the removal of ammonia with a stream of dry nitrogen, the reaction solution was evaporated to dryness *in vacuo*. The resulting residue, which solidified on trituration with ether, was collected by filtration: yield, 67% of crude product. Recrystallization of the crude product from 90% aqueous ethanol (15 ml.) gave the pure material: 135 mg. (38%); m.p. 242°; thin layer chromatography on silica gel H (Merck) using chloroform–methanol (3:1) as the eluent showed a single spot; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 264 (7.5), at pH 7 264 (8.7), and at pH 13 273 (8.4); $\bar{\nu}_{max}$ 3360, 3140 (NH), 3100, 2970, 2935 (CH), 2800–2500 (acidic H), 1675 (C=O), and 1605 (C=C, C=N) cm.$^{-1}$.

Anal. Calcd. for $C_7H_7N_5O$: C, 47.45; H, 3.99; N, 39.53. Found: C, 47.27; H, 4.09; N, 39.53.

Purine-6-acetic Acid Hydrazide (XIX).—Ethyl N-acetylpurine-acetate (XIII, 250 mg., 1 mmole) was dissolved in anhydrous hydrazine (1 ml.) and the resulting solution was allowed to stand at room temperature for 1.5 hr. before it was diluted with ethanol and evaporated to dryness *in vacuo*. Crystallization of the residue was induced by evaporation to dryness with ether and was completed by subsequent trituration with boiling ethanol (15 ml.). The ethanol mixture was cooled and the insoluble solid was collected by filtration: yield of crude product, 70%. Recrystallization of the crude material from 90% aqueous ethanol (10 ml.) gave the pure product: 92 mg. (48%); m.p. 246°; thin layer chromatography on silica gel H (Merck) using methanol as the eluent showed a single spot; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 263 (7.8), at pH 7 264 (9.0), and at pH 13 273 (8.9); $\bar{\nu}_{max}$ 3310 (NH), 3200, 3110, 3050, 2980 (NH and CH), 2800–2650 (acidic H), 1645 (C=O), 1600 and 1535 (C=C, C=N) cm.$^{-1}$.

Anal. Calcd. for $C_7H_8N_6O$: C, 43.74; H, 4.20; N, 43.73. Found: C, 43.97; H, 4.07; N, 43.98.

4-Amino-5H-pyrrolo[3,2-*d*]pyrimidine (9-Deazaadenine, XX).—A mixture of 4-amino-5H-pyrrolo[3,2-*d*]pyrimidine-7-carboxylic acid (XV, 1.58 g., 8.9 mmoles) and powdered glass (3 g.) was spread in a thin layer over the bottom of an erlenmeyer flask (300 ml.). The flask was evacuated to 0.1 mm. and the vacuum was maintained between 0.5 mm. and 0.1 mm. during decarboxylation, which was carried out by spot heating with a free flame. When gas evolution had ceased, the vacuum was released and the reaction mixture was triturated with boiling water (300 ml. in several portions) and filtered through dry Celite. Evaporation of the filtrate to dryness *in vacuo* gave the crude product which was dissolved in propanol (15 ml.) and filtered hot to remove insoluble starting compound. The filtrate was diluted with ether (300 ml.) and the crystalline solid that formed was collected by filtration, washed, and dried to give essentially pure material; yield, 824 mg. (69%). The analytical sample was obtained by recrystallizing a sample of this product from propanol–ether: sublimes with dec. above 260°; thin layer chromatography on silica gel H (Merck) using chloroform–methanol (3:1) showed a single spot; λ_{max} in mμ ($\epsilon \times 10^{-3}$) at pH 1 234 (15.0) and 273 (15.9); at pH 7 228 (21.8), 274 (10.9), and 288 (sh); and at pH 13 229 (23.4), 274 (9.2), and 288 (sh); $\bar{\nu}_{max}$ 3425, 3320 (NH), 3110, 2910, 2850 (NH and CH), 2900–2500 (acidic H), 1665 (NH), 1610, 1545, 1515 (C=C, C=N), and 1450 (CH) cm.$^{-1}$; τ −1.0 (N-5 H), 1.83 (C-2 H), 2.43 and 2.50 (C-6 d, H), 3.28 (N-4 H, 2 protons), and 3.58 and 3.63 (N C-7 d, H) p.p.m.[20]

Anal. Calcd. for $C_6H_6N_4$: C, 53.74; H, 4.51; N, 41.81. Found: C, 53.47; H, 4.64; N, 41.71.

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(20) The ultraviolet and proton magnetic resonance data given agree with those reported by Imai.[11]