(5 mL) was added phosphorus oxychloride (1.01 mL, 11.0 mmol). After the stirring was continued for 24 h at room temperature, the mixture was carefully diluted with water (30 mL) and extracted with ether (3 × 15 mL). The combined extracts were washed successively with 10% hydrochloric acid, water, and aqueous saturated sodium chloride solution and dried ($MgSO_4$). Removal of the solvent gave crude olefin which was purified on a silica gel column eluting with *n*-pentane to give pure olefin **11** as a very sublimable colorless solid: 44 mg (70.5%); mp 140–142 °C; IR (KBr) 3080, 2910, 2870, 1650, 1440, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.78, 4.60 (both t, 2, J = 1.5 Hz, C=CH_2), 2.85–2.40 (m, 2, C_1H, C_3H), 2.4–1.0 (m, 12, other protons); ^{13}C NMR ($CDCl_3$) δ 160.5 (s, 1 C), 101.5 (t, 1 C), 43.3 (d, 1 C), 40.9 (t, 1 C), 40.7 (d, 1 C), 39.9 (t, 1 C), 34.0 (d, 1 C), 30.8 (t, 1 C), 27.8 (d, 1 C), 27.7 (t, 1 C), 23.2 (t, 1 C).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.02; H, 10.98.

4(*e*)-Chloro-2-methyleneadamantane (14). To an ice-cooled and stirred solution of **7b** (402 mg, 2.00 mmol) in anhydrous pyridine (20 mL) was added phosphorus oxychloride (4.8 mL, 52 mmol) portionwise during 10 min. After the stirring was continued for 24 h at room temperature, the mixture was diluted with water (50 mL) and extracted with ether (3 × 20 mL). The combined extracts were washed successively with 10% hydrochloric acid, water, and aqueous saturated sodium chloride solution and dried ($MgSO_4$). Removal of the solvent gave crude olefin which was purified on a silica gel column eluting with *n*-hexane to afford the chloro olefin **14** as crystals: 275 mg (75.3%); mp 57–61 °C; IR (KBr) 3080, 1645, 1450, 1360, 1310, 1280, 1230, 1090, 1080, 880, 800, 780, 760, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (s, 2, C=CH_2), 4.29 (br s, 1, C_4H_{ax}), 2.76–1.33 (m, 12, other protons); ^{13}C NMR ($CDCl_3$) δ 155.0 (s, 1 C), 104.3 (t, 1 C), 67.2 (d, 1 C), 46.3 (d, 1 C), 39.3 (t, 1 C), 38.6 (t, 1 C), 37.5 (d, 1 C), 35.5 (d, 1 C), 32.7 (t, 1 C), 30.6 (t, 1 C), 27.5 (d, 1 C); mass spectrum, m/z (relative intensity) 184 (32.8, M + 2), 182 (100, cm^+), 147 (50.7), 146 (26.9), 131 (73.1), 105 (46.3), 91 (41.8).

Anal. Calcd for $C_{11}H_{15}Cl$: C, 72.32; H, 8.28. Found: C, 72.57; H, 8.03.

Reduction of 14 with Tri-*n*-butyltin Hydride. A mixture of **14** (78 mg, 0.43 mmol), tri-*n*-butyltin hydride (125 mg, 0.43 mmol), and azobis(isobutyronitrile) (1 mg) in cyclohexane (2 mL) was heated under reflux for 20 h. Removal of the solvent and chromatography on a silica gel column (*n*-pentane) afforded methyleneadamantane **15** (50 mg, 79.1%) which was identical with an authentic sample[15] by comparison of the IR and ^1H NMR spectra and GLC retention times.

Oxidation of 14 with Sodium Periodate–Potassium Permanganate. To an ice-cooled and stirred solution of **14** (91 mg, 0.50 mmol) and sodium periodate (429 mg, 1.80 mmol) in acetone (1.5 mL) and water (1.9 mL) was added a solution of potassium permanganate (14 mg, 0.09 mmol) in water (0.5 mL).[16] After the stirring was continued for 14 h at room temperature, the mixture was diluted with water (10 mL) and extracted with ether (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give crude ketone which was purified by preparative TLC (silica gel, CH_2Cl_2) to afford the chloro ketone **16** as colorless crystals [13 mg (14.0%), mp 192–195 °C] whose IR and ^1H NMR spectra were consistent with those reported.[17]

Registry No. 1a, 31603-46-0; **1b**, 66483-55-4; **2a**, 74381-06-9; **2b**, 74381-07-0; **7a**, 74381-08-1; **7b**, 74381-09-2; **8a**, 74381-10-5; **8b**, 74381-11-6; **9**, 74381-12-7; **10**, 74381-13-8; **11**, 74381-14-9; **14**, 74381-15-0; **15**, 875-72-9; **16**, 56781-81-8.

Synthesis of Pyrrolo[3,2-*d*]pyrimidines from Furazano[3,4-*d*]pyrimidines via Enolate and Ene Adducts[1a,b]

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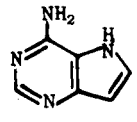
Received October 12, 1979

The reaction of 7-(acylamido)furazano[3,4-*d*]pyrimidines **2** (FZP's) with certain enamines and enolate anions provides intermediates suitable for unequivocal transformation into pyrrolo[3,2-*d*]pyrimidines **11** and **12**. The reaction of **2** with enolate anions appears to proceed via an addition–elimination mechanism. The structures of the FZP–enamine adducts (**7a–h**) and their unusual chemical reactivity are explained in terms of an ene–retroene equilibrium. The proposed ene reaction involves the 6,7 nitrogen–carbon double bond of the FZP as the enophile and the 2-aminopropene fragment present in a limited class of ketone enamines as the ene. The amphoteric nature of the ene adducts was used to advantage in their conversion to derivatives **8**, **9**, and **10**, all of which are incapable of decomposition via the retroene pathway followed by **7a–h**. Intermediates **3–5**, **9**, and **10** were subsequently converted into 11 different pyrrolo[3,2-*d*]pyrimidines without complication by using either zinc in acetic acid or catalytic reduction with a palladium-on-carbon catalyst in acetic acid. In five of the cases where a 2-(CH_3S)FZP was the substrate for reduction, the recently uncovered desulfurizing capability of palladium-on-carbon in hot acetic acid permitted direct isolation of 2-unsubstituted pyrrolo[3,2-*d*]pyrimidines in good yield.

Although there is only one antibiotic of limited use known to contain the pyrrolo[3,2-*d*]pyrimidine ring system (**1**),[2] a substantial number of reports concerning the synthesis of variously substituted examples of this purine isoster have been recently reviewed.[3] At least three reports of new synthetic approaches to this ring system have ap-



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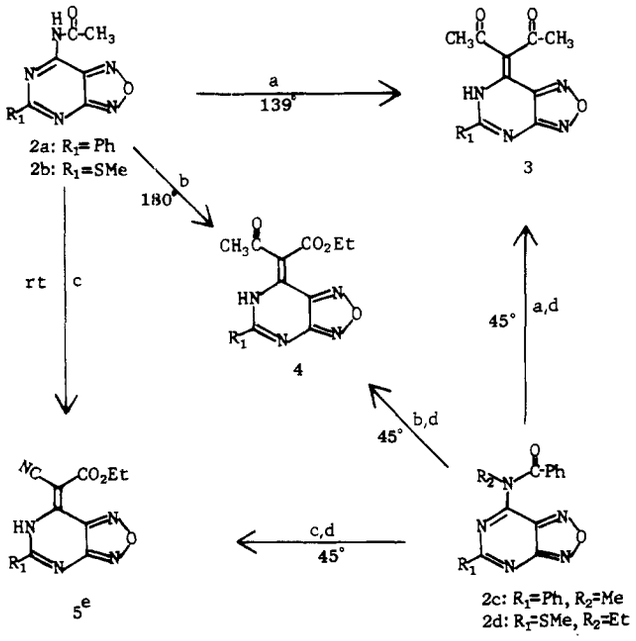
(1) (a) This report is based in part on the Ph.D. Thesis of G.P.B., Princeton University, 1971. (b) This report is based in part on the Ph.D. Thesis of L.E.C., Princeton University, 1976. (c) To whom correspondence should be addressed at the Department of Chemistry, New York University, 4 Washington Place, Room 514, New York, NY 10003.

(2) R. C. Hartenstein and I. Fridovitch, *J. Biol. Chem.*, **242**, 740 (1967).

(3) V. Amarnath and R. Madhav, *Synthesis*, **6**, 837 (1974).

0022-3263/80/1945-3827$01.00/0

Scheme I



[a] Acetylacetone and Et_3N. [b] Ethyl acetoacetate and Et_3N. [c] Ethyl cyanoacetate and Et_3N. [d] THF used as solvent. [e] Methyl ester analogue also prepared from **2b**.

peared subsequently.[4] Among all of the reported synthetic approaches the most elegant appears to the application of Eschenmoser's "alkylative coupling via sulfide contraction" concept[5] to obtain nearly quantitative yields of a limited number of products.[4a]

Results and Discussion

Two new reactions of furazano[3,4-*d*]pyrimidines (FZP's) each produced intermediates which were converted to unequivocally substituted pyrrolo[3,2-*d*]pyrimidines in fair to good overall yields. The first reaction involves interaction of FZP's with enolate anions (Scheme I). These transformations appear to take place by an addition–elimination mechanism.[7] The second route takes advantage of ene adducts formed in good to excellent yields by reaction of FZP's **2a** and **2b** with certain enamines (Scheme II).

Both classes of intermediates were then subjected to reduction–recyclization by using either catalytic hydrogenation or zinc in acetic acid followed by heating. Desulfurized pyrrolo[3,2-*d*]pyrimidines were obtained directly by applying the recently uncovered capability of palladium-on-carbon to simultaneously effect hydrogenation and hydrodesulfurization.[8]

Enolate Reaction. The reactions of FZP **2a** (Scheme I) with the anions of acetylacetone and ethyl acetoacetate both require more vigorous conditions than the parallel reaction of ethyl cyanoacetate. Substitution of **2c** permitted gentle conditions to be effective in all three cases.

Scheme II

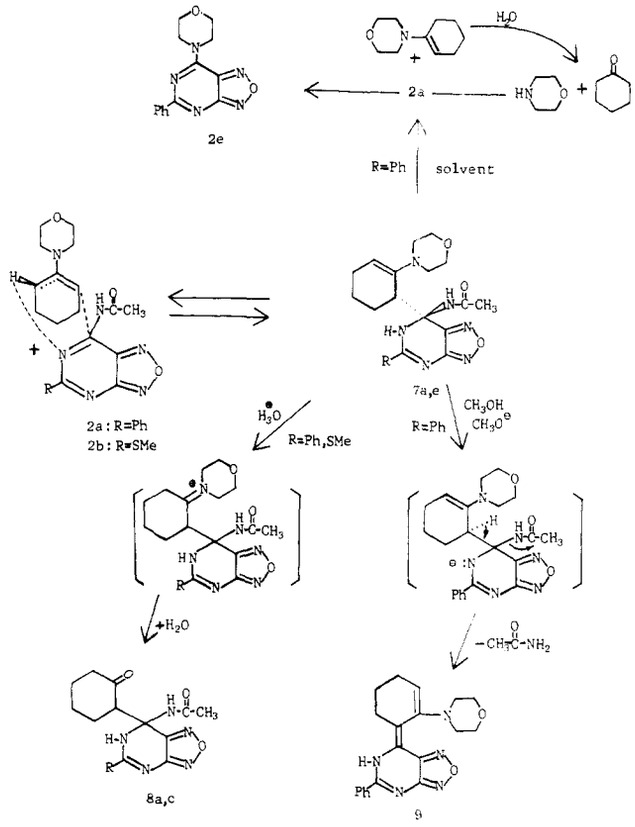
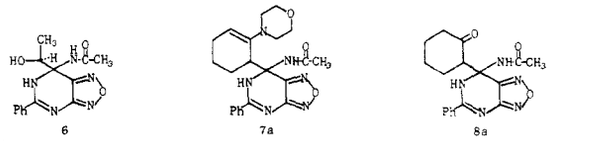


Table I. Comparison of UV Data for 6,7-Dihydro FZP's



	239nm	288nm	235nm	291nm	239nm	284nm
λ_{max}						
log ε	4.07	3.94	4.06	3.91	4.10	4.01

Similarly, substitution of FZP **2d** for **2b** allowed straightforward extension of the more gentle reaction conditions without noticeable competition from nucleophilic displacement of the 5-methylthio substituent, a side reaction observed with some amines.[9] The different pK_a's of the three enolates suggest that the observed reaction rate variations are a function of the presence or absence of acidic N-7 protons[10a] plus variations in anion basicity.[10b]

Enamine Reaction. Mixing solid **2a** with an excess of the redistilled morpholine enamine of cyclohexanone at room temperature invariably produced a white precipitate which did not behave like a normal enamine alkylation product. Repeated attempts to recrystallize **7a** consistently generated **2a** mixed with other products resulting from concomitant enamine decomposition (**2e**).[11] Fortunately, washing the crude solid with dry ether followed by drying at room temperature in vacuo afforded analytically pure **7a**.

(4) (a) H. Fenner and H. Motschall, *Tetrahedron Lett.*, 4185 (1971); (b) T. Murata, T. Sugawara, and K. Ukawa, *Chem. Pharm. Bull.*, **21**, 2571 (1973); T. Murata and K. Ukawa, *ibid.*, **22**, 240, 1212 (1974); (c) S. Senda, K. Hirota, and M. Takahashi, *Heterocycles*, **4**, 461 (1976).

(5) P. Dubs, E. Gotschi, M. Roth, and A. Eschenmoser, *Chimica*, **24**, 34 (1970); A. Eschenmoser, *Q. Rev., Chem. Soc.*, **24**, 366 (1970).

(6) (a) E. C. Taylor, G. P. Beardsley, and Y. Maki, *J. Org. Chem.*, **36**, 3211 (1971), and references therein; (b) L. E. Crane, Y. Maki, and G. P. Beardsley, submitted for publication.

(7) E. C. Taylor, "Principles of Heterocyclic Chemistry", American Chemical Society, Washington DC, 1974, American Chemical Society Tape Course, Part I, pp 117–120.

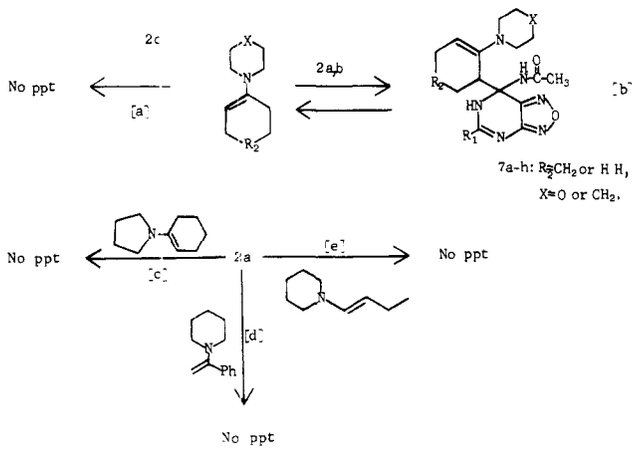
(8) See: ref **6b**; L. E. Crane, submitted for publication.

(9) Unpublished details communicated to me by G.P.B.

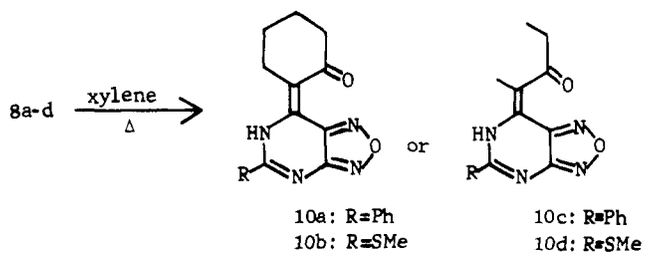
(10) A. Albert and E. P. Sargent, "Ionization Constants of Acids and Bases", Wiley, 1962, p 132; the pK_a of succinimide is reported to be 9.62, a value which is probably close to the actual pK_a of **2a**. (b) J. March, "Advanced Organic Chemistry", McGraw-Hill, New York, 1968, pp 219–221; averaging the pK_a values for malononitrile and diethyl malonate yields an estimated pK_a of 12.5 for ethyl cyanoacetate.

(11) This was first observed by Y.M. and G.P.B., unpublished reports. Subsequently L.E.C. observed that an NMR sample of **7a** in Me_2SO-d_6 permitted to stand at room temperature for a few weeks yielded large cubic crystals of **2a**.

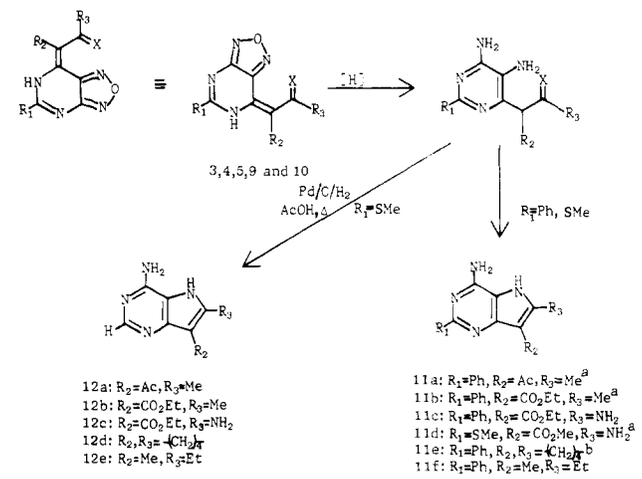
Scheme III



Scheme IV



Scheme V



[a] Reduction with zinc in acetic acid. [b] Prepared starting with **9**.

The UV spectra of freshly prepared solutions of **7a** and of a white compound produced by gentle acid hydrolysis of **7a** (**8a**) are nearly identical with the UV spectrum of photoadduct **6**,[12] which suggests identical chromophores in all three compounds and the analogues **7b–h** and **8b–d** (Table I). Moreover, the ^{1}H NMR spectra of the ene adducts all require the presence of a trisubstituted double bond in the enamino group (see NMR data for **7a** and **7d**), a finding consistent with the characteristic double bond migration of the ene reaction. In addition, the spontaneous decomposition to starting materials, following dissolution in a neutral solvent, was confirmed by the appearance of the acetyl methyl resonance of either **2a** or **2b** in every proton spectrum obtained, starting with analytically pure samples of **7a–h**. Reversibility in enamine alkylations is not a common occurrence,[13] but the reversibility of the ene reaction is well documented.[14]

Treatment of **7a** with sodium methoxide in refluxing methanol caused loss of acetamide to afford **9** in nearly quantitative yield (Scheme II). Alternatively, mixing **7a** with 50% aqueous acetic acid at room temperature affords **8a** in high yield, probably via the iminium ion pictured in Scheme II. It appears that both of these reactions involved rapid removal of a functional group required for retroene decomposition, thereby effectively suppressing the retroene route in favor of alternate pathways.

It has been suggested that **7a–h** may be formed via an aldol mechanism.[15] The operation of an aldol–retroaldol equilibrium in these cases is cast into doubt by the observation that **7a** can be prepared in 75–80% yield in three different reaction media: (1) in neat enamine, (2) in 1:1 enamine–dry acetonitrile, or (3) in 1:1:1 enamine–dry acetonitrile–glacial acetic acid.[16]

The formation of adducts like **7a** occurs within limited classes of FZP's and of enamines. The piperidine enamines of butyraldehyde and acetophenone, FZP **2c**, and the pyrrolidine enamine of cyclohexanone (Scheme III) all failed to generate a precipitate. However, the piperidine and morpholine enamines of 3-pentanone and cyclohexanone all produced adducts with **2a** and **2b** without difficulty at room temperature. The substantially greater basicity of pyrrolidine enamines[17] suggests that the ene pathway in reaction [c] was probably suppressed by a competitive acid–base reaction.[10] The other failures all seem consistent with the structural requirements ([d] and [e]) and steric sensitivity ([a]) of an ene–retroene equilibrium.[18]

The thermolysis of ketones **8a–d** (Scheme IV) caused the elimination of acetamide, producing unsaturated ketones **10a–d** in good to excellent yields. The structures for **10a–d** were assigned the keto form on the basis of a parallel with the structure of **9** and the similarity of the UV spectra recorded for **9** and **10a–d**. The ^{1}H NMR spectrum of **9** requires maintenance of the enamine function, while the drastic downfield shift (12.67–14.4 ppm from **9** to **10b**) of a D_2O-exchangeable one-proton resonance seems consistent with the greater electron-withdrawing effect of the carbonyl function in **10b** plus an intramolecular hydrogen bond with the N-6 proton. The low carbonyl stretching frequencies (1620–1650 cm^{-1}), the absence of a free NH or OH absorption band at 3500 cm^{-1}, and the very weak hydrogen-bonding absorption band observed in only one case (**10b**, 3050 cm^{-1}) are consistent with the structures assigned to **10a–d**.[21]

Pyrrolo[3,2-*d*]pyrimidines. As a consequence of our inability to readily isolate intermediates analogous to **9** as solids, the hydrolysis–thermolysis sequence leading from **7a–h** to **10a–d** is the recommended route to substrates

(12) E. C. Taylor, Y. Maki, and B. E. Evans, *J. Am. Chem. Soc.*, **91**, 5181 (1969).
(13) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. C. Thweatt, *J. Org. Chem.*, **29**, 813 (1964).
(14) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).
(15) (a) Private communication with Professor G. Stork. (b) The possibility that some enamine alkylations by electron-deficient unsaturation may proceed by no-mechanism reactions is suggested by the organization of a review: O. Tsuge and A. Inabe, *Kagaku No Ryoiki*, **26**, 191 (1972).
(16) A field desorption (FD) mass spectrum of **7a**, generously supplied by Professor C. C. Sweeley of Michigan State University, seems to support this view. Although a more complete study is required before publication of a detailed report, it appears that protonated **7a** does not decompose to produce either protonated enamine or protonated **2a**, an indication that neutral **7a** is neither formed nor decomposed via a cationic intermediate.
(17) M. E. Kuehne and L. Foley, *J. Org. Chem.*, **30**, 4280 (1965).
(18) The greater bulk of the 7-substituent in **2c** is the probable cause of its failure to react as an enophile.

suitable for conversion to pyrrolo[3,2-*d*]pyrimidines. The reduction–recyclization sequence illustrated in Scheme V was effected with either zinc in acetic acid or by catalytic hydrogenation with palladium-on-carbon. All five of the methylthio-substituted substrates were converted directly into 2-unsubstituted pyrrolo[3,2-*d*]pyrimidines **12a–e** in yields ranging from 54 to 69% by application of the recently reported desulfurizing capability of palladium-on-carbon in hot acetic acid.[8]

Conclusion

The unambiguous construction of 11 different pyrrolo[3,2-*d*]pyrimidines by two separate pathways beginning with furazano[3,4-*d*]pyrimidines represents another illustration of the synthetic utility of the FZP ring system.[6a] With overall yields in the range of 24–70%,[19] these synthetic routes are both flexible and reasonably efficient. The nature of the reaction of FZP's **2a** and **2b** with enamines clearly indicates that some heterocycles with electron-deficient imino groups and certain enamines can be effective participants in the no-mechanism ene reaction. The preparation of additional fused pyrimidine derivatives via FZP intermediates and further exploration of the ene reaction of enamines are areas of continuing interest.

Experimental Section

Microanalyses were performed by Galbraith Microanalytical Laboratories, Baron Consulting Co., Gifu College of Pharmacy, and the Microanalytical Laboratories of Hoffmann-LaRoche Co., Inc. Melting points are uncorrected. NMR spectra were determined in the solvent specified by using a Varian A60A spectrometer. UV spectra were obtained with a Cary Model 11 recording spectrophotometer. All precise mass data were obtained with an AEI-MS9 double-focusing mass spectrometer. Electron ionization (EI) mass spectra were obtained by using the direct-inlet probe of a Du Pont 21-490 GC/MS with a 21-094 MS data system. IR spectra were recorded with a Perkin-Elmer 237B grating spectrophotometer.

7-(Acylamino)furazano[3,4-*d*]pyrimidines (2). The published procedures of Taylor et al.[6a] provided direct access to the four compounds used as starting materials in this work. Analytical data gathered for the three new derivatives isolated are listed in Table II.[19,20]

7-(Diacetylmethyl)-5-phenylfurazano[3,4-*d*]pyrimidine (3a).[20] **Method A.** A mixture of **2a** (1.0 g, 3.92 mmol), 8 mL of 2,4-pentanedione, and 0.5 mL of Et_3N was heated at reflux (139 °C) for 4 h. The reaction mixture was concentrated under reduced pressure and then diluted with a 2:1 mixture of *n*-heptane and ether. After several hours at room temperature, the crystals deposited were collected and recrystallized from methanol to give 0.79 g (68% of theory) of light yellow needles, mp 189–190 °C.

Method B. A portion of **2c** (2.0 g, 6.04 mmol) was dissolved in a mixture of 10 mL of acetylacetone, 5.0 mL of Et_3N, and 20 mL of dry THF and heated at reflux for 96 h. The solvent and volatile reactants were removed in vacuo (0.02 mmHg) to produce a crude yellow solid weighing 1.0 g (56% of theory). A sample of this material was found to be identical with authentic **3a** produced by method A: NMR ($CDCl_3$) δ 2.35, 2.66 (3 H + 3 H, acetyl CH_3), 7.5–8.3 (5 H, Ph), 14.3 (1 H, NH or OH).

Preparation of Enamines. All enamines were prepared by the method[22] of White and Weingarten except for 1-morpholino-1-cyclohexene which was purchased from Aldrich Chemical Co. All enamines were carefully vacuum distilled (or redistilled) under a nitrogen atmosphere before use and stored under nitrogen in a refrigerator (Airless Flasks, Kontes Glass Co.) without noticeable decomposition.[23]

7-(Acetamido)-7-(2-morpholinocyclohex-2-enyl)-5-phenyl-6,7-dihydrofurazano[3,4-*d*]pyrimidine (7a).[20] A portion of recrystallized **2a** (1.0 g, 3.92 mmol) was mixed with 5 mL of redistilled 1-morpholino-1-cyclohexene, 5 mL of dry acetonitrile, and 5 mL of glacial acetic acid. The initially clear solution was allowed to stir overnight at room temperature. The thick pasty mixture produced was diluted with 15–20 mL of ether and vigorously agitated, and the resultant suspension was subjected to vacuum filtration. After being washed with several small portions of ether, the solid residue was dried under vacuum (room temperature, 0.02 mmHg) for 1 h. The white powdery product weighed 1.26–1.35 g (75–80% of theory):[24] mp 150–155 °C dec; NMR (Me_2SO-d_6) δ 1.9 (3 H, CH_3C=O), 5.5 (1 H, t, CH_2CH=C), 7.45–8.1 (5 H, Ph).

7-(Acetamido)-5-phenyl-7-(1-methyl-2-piperidinobut-2-enyl)-6,7-dihydrofurazano[3,4-*d*]pyrimidine (7d).[20] A portion of **2a** (0.50 g, 1.96 mmol) was added to a mixture of 5 mL of dry acetonitrile and 5 mL of 3-piperidino-2-pentene and the mixture stirred overnight at ice bath temperature. Vacuum filtration afforded 0.65 g of a white powdery solid (81% of theory), mp 115–116 °C dec. Drying in vacuo (0.02 mmHg) produced analytically pure product:[25,26] NMR (Me_2SO-d_6) δ 1.27, 1.58 (3 H + 3 H, 2 d, CH_3CHC or CH_3CH=C), 2.0–3.3 (10 H, piperidino), 4.4, 4.79 (1 H + 1 H, 2 q, CH_3CHC or CH_3CH=C), 7.4–8.2 (5 H, Ph), 8.68 (1 H, NH), 9.08 (1 H, NH).

7-(Acetamido)-5-(methylthio)-7-(1-methyl-2-oxobutyl)-6,7-dihydrofurazano[3,4-*d*]pyrimidine (8d).[20] A portion of **7h** (500 mg, 1.32 mmol) was mixed with 25 mL of 50% aqueous acetic acid. After the mixture was stirred for 10 min at room temperature, vacuum filtration afforded 250–275 mg of a white powdery solid (61–67% of theory), mp 207–208 °C. The vacuum-dried product (60 °C, 12 h, 0.02 mmHg) was analytically pure: NMR (Me_2SO-d_6) δ 0.84 (3 H, t, CH_3CH_2), 1.32 (3 H, d, CH_3CH), 1.79 (3 H, CH_3C=O), 2.38 (3 H, SCH_3), 3.43 (1 H, q, CH_3CH), 8.92 (2 H, 2 NH).

7-(2-Morpholinocyclohex-2-enylidene)-5-phenyl-6,7-dihydrofurazano[3,4-*d*]pyrimidine (9).[20] A portion of **7a** (1.82 g, 4.31 mmol) was mixed with a previously prepared solution of 460 mg of sodium metal in 15 mL of methanol and the mixture refluxed for 20 min. When the homogeneous yellow solution was cooled to room temperature, yellow needles formed which were isolated by vacuum filtration. After being washed with a small portion of dry methanol, the yellow crystals were dried under vacuum (60 °C, 1 h, 0.02 mmHg) and subsequently found to weigh 1.51 g (96% of theory), mp 250–251 °C dec. The analytical sample was prepared by recrystallization from xylene: NMR ($CDCl_3$) δ 1.5–4.0 (14 H, morpholino and cyclohexyl CH_2), 5.58 (1 H, t, CH_2CH=C), 7.5–8.2 (5 H, Ph), 12.67 (1 H, NH); UV (CH_3OH) 237 nm (ϵ 4.25), 262 (4.32), 383 (4.12).

7-(1-Methyl-2-oxobutylidene)-5-phenyl-6,7-dihydrofurazano[3,4-*d*]pyrimidine (10b).[20] A portion of **8b** (410 mg, 1.2 mmol) was added to 10 mL of xylene and the mixture refluxed for 2 h. Removal of the xylene in vacuo afforded 280 mg of yellow crystals (82% of theory), mp 184–185 °C. The analytical sample was prepared by recrystallization from absolute ethanol: NMR ($CDCl_3$) δ 1.20 (3 H, t, CH_3CH_2), 2.51 (3 H, CH_3), 1.69 (2 H, q, CH_3CH_2), 7.5–8.4 (5 H, Ph), 14.4 (1 H, NH); UV (CH_3OH) 241 nm (ϵ 4.17), 275 (4.06), 387 (4.15).

7-Acetyl-4-amino-6-methyl-2-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (11a).[20] A portion of **3a** (0.5 g, 1.69 mmol) was stirred vigorously with a mixture of 1.0 g of zinc dust in 15 mL of glacial acetic acid for 30 min. After 2 h at reflux the reaction mixture was cooled and filtered. The filtrate was evaporated to dryness

(19) No attempt was made to optimize yields.
(20) Microanalytical and spectral data for all new compounds cited in this paper appear as supplementary material.
(21) K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, 1962, pp 30, 43.
(22) W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).
(23) Under these conditions some of the enamines turned a pale yellow, but this had no noticeable impact on their chemical activity.
(24) In separate reports Y.M. and G.P.B. reported yields in this range for reactions run in the absence of solvent: ref **1b** and unpublished reports.
(25) The preparation had to be repeated once to obtain an analytically pure sample.
(26) In cases where **2b** is the heterocyclic coreactant, the ene adduct occurs as an oily layer at the bottom of the reaction flask on occasion. The oily products were readily crystallized by the addition of hexane or pentane followed by swirling of the mixture with the flask immersed in an ultrasonic bath at room temperature.

in vacuo and the residue shaken with a small quantity of water. The precipitate formed was isolated by filtration and recrystallized from ethanol to afford 0.21 g (48% of theory) of colorless crystals, mp >300 °C.

Derivative. Compound **11a** was warmed briefly in acetic anhydride. The reaction mixture was then evaporated to dryness and the residue crystallized with ethanol to afford the 4-acetamido derivative: mp 277–278 °C; NMR (Me_2SO-d_6) δ 2.37 (3 H, 6-CH_3), 2.72 and 2.87 (3 H + 3 H, acetyl CH_3's), 7.5–8.4 (5 H, Ph), 9.04 and 9.27 (1 H + 1 H, NH's).

4,6-Diamino-7-(ethoxycarbonyl)-2-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (11c).[20] A portion of **5a** (1.0 g, 3.23 mmol) dissolved in 50 mL of glacial acetic acid was hydrogenated in the presence of 50 mg of 10% palladium-on-carbon at room temperature under 1 atm of hydrogen until the hydrogen uptake ceased. The mixture was stirred at room temperature for an additional 24 h. The catalyst was removed by vacuum filtration and the filtrate evaporated in vacuo. The residual oil was shaken with a small quantity of water, and the resulting suspension was adjusted to neutral pH by the addition of aqueous ammonia. The solid generated was collected by filtration and recrystallized from ethanol to give 0.86 g of colorless crystals (83% of theory): mp 258–262 °C; NMR (Me_2SO-d_6) δ 1.36 (3 H, t, CH_3CH_2), 4.28 (2 H, q, CH_3CH_2O), 7.5–8.4 (5 H, Ph).

7-Acetyl-4-amino-6-methyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (12a). A portion of **3b** (400 mg, 1.5 mmol) and 250 mg of 10% palladium-on-carbon were mixed with 10 mL of glacial acetic acid and then attached to an atmospheric pressure hydrogenation apparatus. Following purging of oxygen the reaction mixture was heated to slightly less than 100 °C with a preheated oil bath and then stirred vigorously for 4 h at 90–100 °C. Hydrogen adsorption appeared to cease after 12 min. The reaction mixture was then permitted to cool to room temperature, and the catalyst was separated by vacuum filtration. Evaporation of the solvent in vacuo afforded a clear tan oil which crystallized when treated with a small amount of ethyl ether. The solid was isolated by filtration and dissolved in water, and the resultant solution was filtered. The addition of excess ammonia to the filtrate generated a precipitate which when it was filtered and dried was found to weigh 195 mg (69% of theory); mp 350–51 °C. The analytical sample was prepared by reprecipitation from a slightly acidic aqueous solution with excess ammonia: NMR (CD_3CO_2D) δ 2.63, 2.86 (3 H + 3 H, CH_3C=O and 6-CH_3), 8.52 (1 H, C^2H); mass spectrum (EI), *m/e* (relative, intensity) 191 (1.3), 190 (10.3, M^+), 175 (11.3), 95 (10.3), 69 (94.8),[27] 45 (100.0); precise mass (calcd/found) 190.085 456/190.085 318.

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Registry No. 2a, 30720-60-6; **2b**, 74366-57-7; **2c**, 74366-58-8; **2d**, 74366-59-9; **3a**, 74366-60-2; **3b**, 74366-61-3; **4a**, 74366-62-4; **4b**, 74366-63-5; **5a**, 74366-64-6; **5b**, 74366-65-7; **5c**, 74366-66-8; **6**, 23582-09-4; **7a**, 74366-67-9; **7b**, 74366-68-0; **7c**, 74366-69-1; **7d**, 74366-70-4; **7e**, 74366-71-5; **7f**, 74366-72-6; **7g**, 74366-73-7; **7h**, 74366-74-8; **8a**, 74366-75-9; **8b**, 74366-76-0; **8c**, 74366-77-1; **8d**, 74366-78-2; **9**, 74366-79-3; **10a**, 74366-80-6; **10b**, 74366-81-7; **10c**, 74366-82-8; **10d**, 74366-83-9; **11a**, 74366-84-0; **11a** 4-acetamido derivative, 74366-85-1; **11b**, 74366-86-2; **11b** 4-acetamido derivative, 74366-87-3; **11c**, 74366-88-4; **11d**, 74366-89-5; **11e**, 74366-90-8; **11f**, 74366-91-9; **12a**, 74366-92-0; **12b**, 74366-93-1; **12c**, 74366-94-2; **12d**, 74366-95-3; **12e**, 74366-96-4; 2,4-pentanedione, 123-54-6; 1-morpholino-1-cyclohexene, 670-80-4; 3-piperidino-3-pentene, 21086-43-1.

Supplementary Material Available: Tables containing physical properties and analytical data for compounds **2b-d** (Table II), **3**, **4**, **5** (Table III), **7a–h** (Table IV), **8a–d**, **9** (Table V), **10a–d** (Table VI), **11a–f**, and **12a–e** (Table VII) (7 pages). Ordering information is given on any current masthead page.

(27) The mass spectrum of this compound was obtained by using a sample of its trifluoroacetate salt which is reflected by this signal.

New Histamine and Histidine Analogues via Transformations of the 2-Trifluoromethyl Group

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α-*N*-Benzoyl-2-(trifluoromethyl)histamine has been transformed, via a difluorodiazafulvene intermediate, into 2-carboxy- and 2-(carbomethoxy)histamine. 2-Carboxy-L-histidine was prepared by a similar route. 2-(Carbomethoxy)-L-histidine was prepared by methanolysis of α-*N*-(*tert*-butoxycarbonyl)-2-(trifluoromethyl)-L-histidine and acid hydrolysis of the intermediate ortho ester. 2-Cyanohistamine and 2-cyano-L-histidine are best prepared by ammonolysis of the corresponding α-*N*-(*tert*-butoxycarbonyl)-2-(trifluoromethyl)imidazoles and acid cleavage of the protecting group. During the hydrolysis of *N*-benzoyl protecting groups in hot, aqueous mineral acid, decarboxylation of 2-carboxyimidazoles occurs gradually; this side reaction is repressed by use of concentrated acid.

The histidine analogue 2-fluoro-L-histidine exhibits a wide range of interesting biological properties: the compound is incorporated into new protein at the expense of histidine—both in bacterial[2] and in mammalian[3] systems; it also shows antibacterial,[2,4] antiviral,[5] and antileukemic[6]

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