Pyrido[2,3-*d*]pyrimidines. IV. Synthetic Studies Leading to Various Oxopyrido[2,3-*d*]pyrimidines

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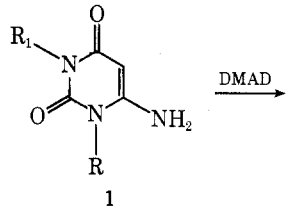
The use of dimethyl acetylenedicarboxylate (DMAD) in protic solvents for the synthesis of a number of new pyrido[2,3-*d*]pyrimidines is described. The structures of the products as 5-carbomethoxy-7-oxopyrido[2,3-*d*]pyrimidines were established by unequivocal synthetic procedures. It was found that a methyl group at N-1 of the starting 6-aminouracils exerts a profound influence on the course of the reaction with DMAD in aprotic solvents to give either C-5 acylation or C-5 alkylation. In protic media, on the other hand, only the products of C-5 alkylation were obtained. Certain mechanistic aspects of the protic vs. aprotic reactions are developed.

Interest has been stimulated in oxo derivatives of pyrido[2,3-*d*]pyrimidines by the observation of significant antitumor activity against Walker muscular carcinosarcoma in rats of 4-oxo- (NSC 112518) and 2,4-dioxopyrido[2,3-*d*]pyrimidine (NSC 112519).[1] Earlier studies directed toward the reactions of dimethyl acetylenedicarboxylate with a number of 6-aminouracil derivatives in aprotic media revealed that all 1-substituted 6-aminouracils studied gave the corresponding 6-amino-5-(3-carbomethoxy-2-propynoyl)uracils rather than the expected pyrido[2,3-*d*]pyrimidines.[2] The object of the present report is to describe similar reactions carried out in protic solvents which do lead to pyrido[2,3-*d*]pyrimidines, to prove the structures of the products, and to consider certain interesting mechanistic aspects of the protic vs. aprotic reactions.

Dimethyl acetylenedicarboxylate (DMAD) has found extensive use in heterocyclic synthesis, both because of its high reactivity and because reaction at the triple bond by either 1,3-dipolar addition[3] or by Michael addition followed by cyclization through the β-ester function[4] provides the double bond requisite to a heteroaromatic system.

Unsubstituted and *N*-methyl derivatives of 6-aminouracil (**1**) provide a particularly interesting case for study, since in addition to the acylation reaction previously described,[2] Michael addition may occur either by attack of C-5 on the triple bond to give **2** after cyclization or by attack of N-6 ultimately yielding **3**.[5]



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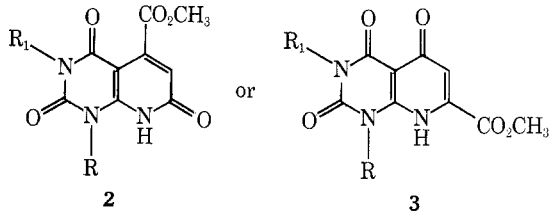
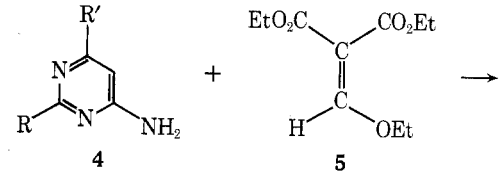


2 or **3**

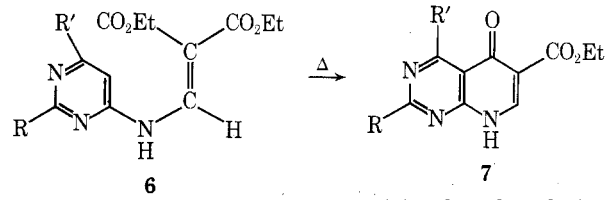
a, R = R$_1$ = H
b, R = CH$_3$; R$_1$ = H
c, R = R$_1$ = CH$_3$
d, R = H; R$_1$ = CH$_3$

Reaction of 6-amino-1,3-dimethyluracil (**1c**) with DMAD in refluxing methanol gave a 64% yield of a compound readily identifiable as a pyrido[2,3-*d*]pyrimidine by elemental analysis, uv, and ^{1}H NMR spectroscopy. Signals attributable to C-5 H (δ 4.72) and the amino group (δ 6.72) present in **1c** disappeared and the product spectrum consisted of singlets for two *N*-methyl groups (δ 3.48, 3.23), one *O*-methyl (δ 3.85), and C-6 H (δ 6.46). It was necessary to determine, however, which of the two possible isomers **2c** or **3c** was obtained.

A well-known method for the preparation of 5-oxo-6-carbethoxypyrido[2,3-*d*]pyrimidine[6,7] is the Gould–Jacobs reaction, which consists of the reaction of an appropriately substituted 6-aminopyrimidine (e.g., **4**) with diethyl ethoxymethylene malonate (**5**). The intermediate **6** is then thermally cyclized to the 6-carbethoxy-5-oxopyrido[2,3-*d*]-pyrimidine **7** Because intermediates of type **6** are readily characterized by ^{1}H NMR spectroscopy,[6] the structure of the product (**7**) as a 5-oxo rather than a 7-oxo derivative is unequivocally established.



4 **5**

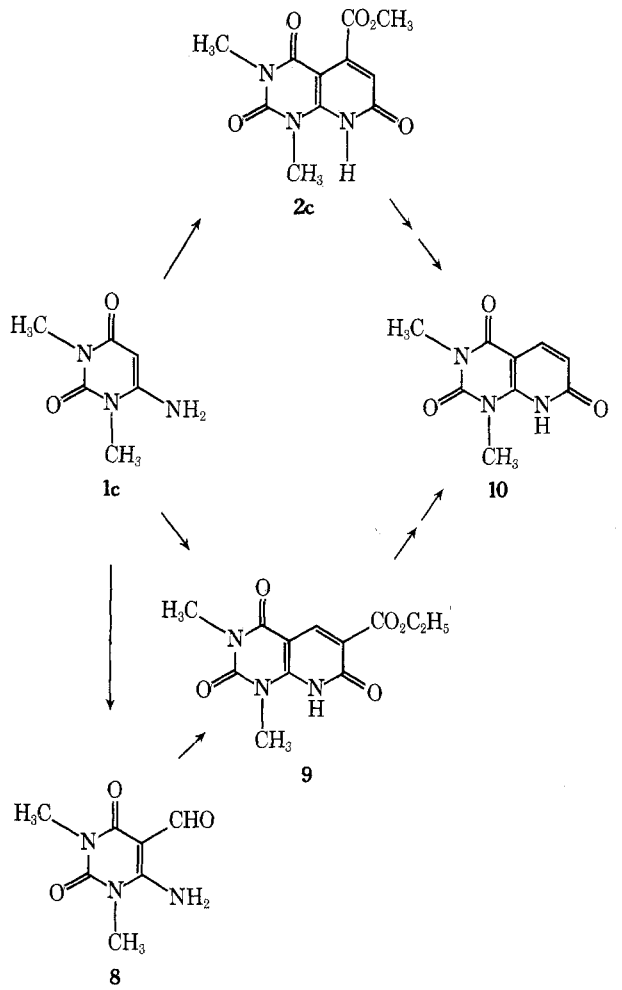


6 **7**

Saponification of **2c** or **3c** followed by decarboxylation would yield, respectively, the 1,3-dimethyl-2,4,7-trioxo- or 1,3-dimethyl-2,4,5-trioxopyrido[2,3-*d*]pyrimidine. It was reasoned that submission of **1c** to the conditions of the Gould–Jacobs reaction should yield 6-carbethoxy-1,3-dimethyl-2,4,5-trioxopyrido[2,3-*d*]pyrimidine which, upon saponification and decarboxylation, should give the 5-oxo isomer and enable by direct comparison the structure assignment of **2c** vs. **3c**. In fact, when this procedure was undertaken, a trioxopyrido[2,3-*d*]pyrimidine identical with the decarboxylated **2c** (**3c**) was obtained, thereby suggesting structure **3c** as correct. However, it was impossible to isolate an intermediate analogous to **6**; either no reaction occurred or only the cyclized material was obtained.

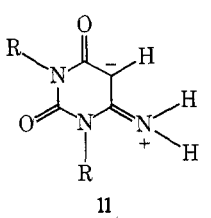
A rigorous proof of structure of the condensation product of **1c** and **5** was therefore undertaken as shown in Scheme I. Condensation of 6-amino-1,3-dimethyl-2,4-dioxo-5-formylpyrimidine (**8**)[8] with diethyl malonate in the presence of piperidine gave unequivocally the 6-carbethoxy-1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**9**), which was found to be identical in every respect with the

Scheme I



reaction product of **1c** and **5** by elemental analysis, uv, ^{1}H NMR, ir, and TLC. These reaction sequences, outlined in Scheme I, conclusively demonstrate that the reaction of **1c** with DMAD yields **2c** rather than **3c** and the saponification and decarboxylation of **2c** and **9** give the 7-oxo derivative **10**.

It is clear that caution must be used in proposing structures by analogy to other reactions; the conversion of **1c** to **9** appears to be the first reported case of carbon alkylation rather than nitrogen alkylation by diethyl ethoxymethylene malonate in the aminopyrimidine series. These reactions emphasize the importance of structural modification on pyrimidine reactivity and suggest that resonance form **11** must play a substantial role in determining C vs. N reactivity.



11

In refluxing aqueous solution DMAD reacted with 1-methyl-6-aminouracil (**1b**) to give 5-carbomethoxy-1-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**2b**). The structure of **2b** was established by the marked similarity of the ^{1}H NMR spectra of **2b** and **2c** and of the uv spectra of the neutral and monoanionic species of both molecules (vide infra). From the reaction of 6-aminouracil (**1a**) under the same conditions only one product (**2a**) was isolated in

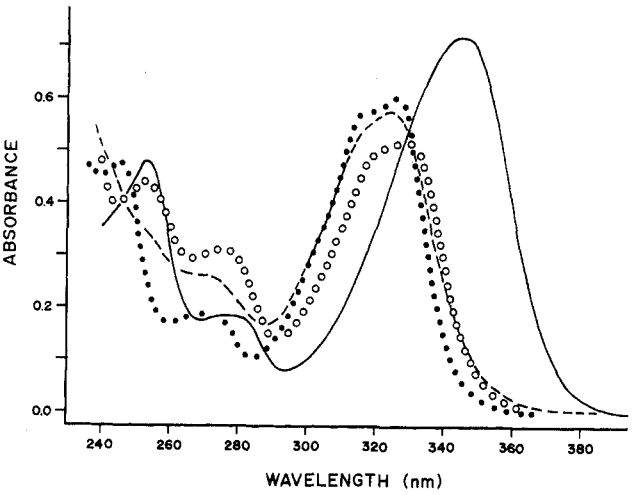
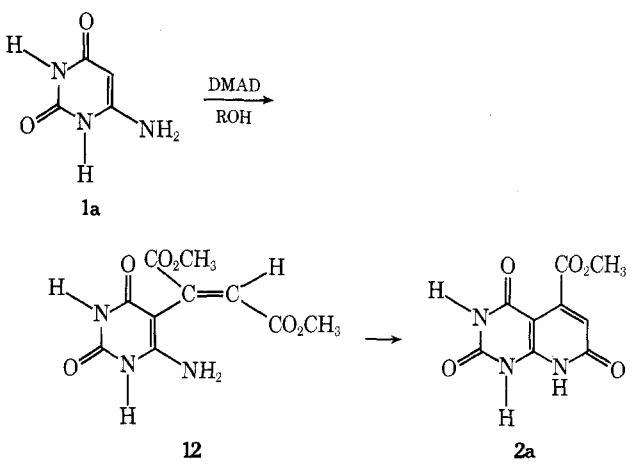


Figure 1. Uv spectra of dianion of **2a** (---), **2b** (●), **2d** (○), and **15** (—).

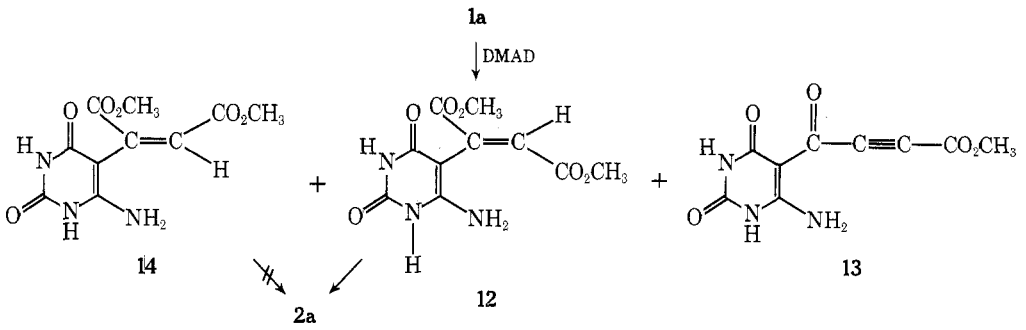
52% yield. Unequivocal determination of the structure of **2a** was accomplished by carrying out a similar reaction in methanol at room temperature, from which the intermediate fumarate **12** was isolated. Compound **12** was readily



1a **12** **2a**

characterized by its ^{1}H NMR spectrum, which consisted of two downfield, D_2O-exchangeable singlets at δ 10.22 and 10.37 corresponding to the ring NH groups, a sharp singlet at δ 6.65 corresponding to the lone fumarate olefinic proton[9] (replacing the C-5 H signal at δ 4.58 in **1a**), a broad, two-proton singlet at δ 6.22 (amino group), and two *O*-methyl signals at δ 3.68 and and 3.65. Upon brief heating in DMF, **12** was quantitatively converted to **2a**.

When DMAD and **1a** were allowed to react in $(CD_3)_2SO$ and the reaction was followed by ^{1}H NMR spectroscopy a different and mechanistically interesting pattern emerged. Three compounds were formed in significant amounts in the approximate ratios of 5:1.5:1. Of the two minor products, the one present in greater quantity was identified as the fumarate derivative (**12**) described above by virtue of the identity of their ^{1}H NMR signals and thin layer chromatographic mobilities. The reaction was run on a larger scale in $(CH_3)_2SO$; the other minor compound was isolated and shown by ^{1}H NMR and elemental analysis to be 6-amino-5-(β-carbomethoxypropynoyl)uracil (**13**). As previously described for the reaction product of **1c** with DMAD in aprotic media,[2] the ^{1}H NMR spectrum of **13** revealed the presence of an *O*-methyl group (δ 3.75) and the loss of the signal for C-5 H. The major product isolated in 41% yield was isomeric to **12** but the olefinic proton signal appeared in the ^{1}H NMR spectrum at δ 5.95 rather than the δ 6.65 signal observed for **12**. When the two isomers

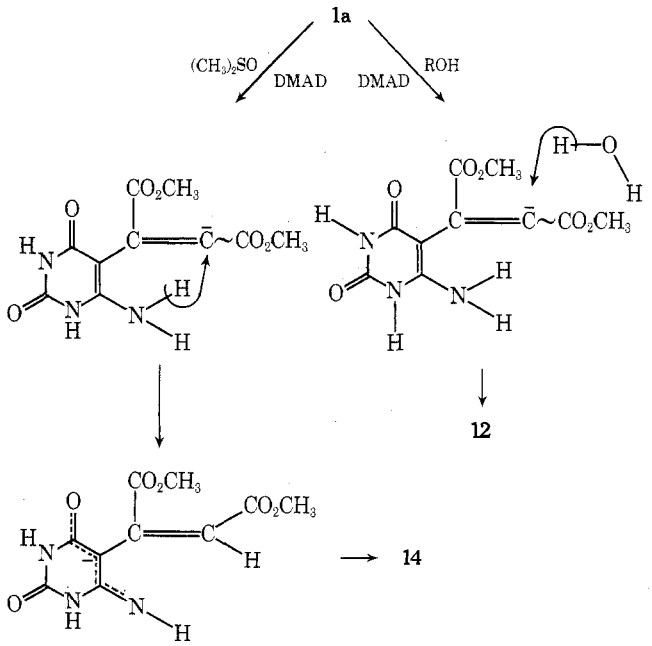


were subjected to heating in DMF compound **12**, as indicated above, readily and quantitatively cyclized to **2a**; under the same conditions **14** underwent no reaction and under forcing conditions gave only a complex mixture of products, thus establishing the stereochemistry of the isomeric olefins.

The solvent dependence of the reaction of 6-aminouracils (**1**) with DMAD is remarkable and only partially understood. There are three major reaction types to consider, i.e., alkylation to give a maleate adduct (e.g., **14**), alkylation yielding a fumarate adduct (e.g., **12**), and acylation to give propynoyl derivatives such as **13**. The reactions appear to be classifiable according to (a) presence or absence of an N-1 substituent and (b) the availability of protons from solvent.

In the absence of a substituent at N-1, for example with **1a**, a 7-oxo-5-carbomethoxypyrido[2,3-*d*]pyrimidine (**2a**) is the major product in water, whereas the maleate adduct **14** predominates in a largely (the solvent was not rigorously dried) aprotic solvent such as $(CH_3)_2SO$. This observation may be readily explained by intramolecular transfer of a proton from the 6-amino group to the Michael anion as illustrated in Scheme II. In water, proton transfer from the solvent shell about the anion presumably permits more rapid formation of the fumarate isomer **12**.

Scheme II



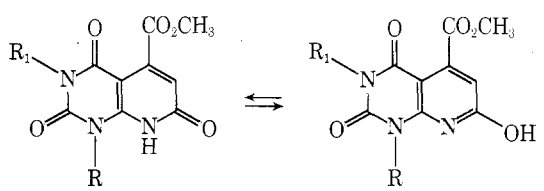
The effect of an N-1 substituent, for example the case of **1c**, is more difficult to understand. In protic media such as water or methanol all the 6-aminouracils are converted by DMAD largely to pyrido[2,3-*d*]pyrimidines **2**. In aprotic media, however, the presence of an N-1 substituent causes acylation to occur essentially to the exclusion of alkylation, in sharp contrast to the reaction of **1a** in which the acylation product comprises only about 15% of the reaction mixture. This appears to be a unique phenomenon which has considerable importance in determining optimum conditions for the use of DMAD in synthetic heterocyclic chemistry. It is being intensively studied at this time and will be the subject of a further report in the near future.

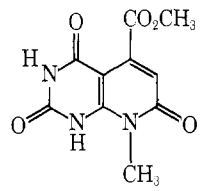
It was of interest to determine whether pyrido[2,3-*d*]pyrimidines bearing a 7-oxo group as the only pyridine ring substituent could be obtained directly rather than through the low-yield decarboxylation procedure described above. It was determined that the reaction of **1c** with ethyl propiolate in refluxing water did indeed give a good yield of **10** directly, identical in all respects with the products obtained from the decarboxylation of **2c** and **9**.

It has been widely assumed in heterocyclic chemistry that substitution of methyl for hydrogen in a heteroaromatic lactam system results in little change in the uv spectrum; numerous examples have been cited[10] using *N*-methyl and *O*-methyl derivatives to show that α- and γ-oxo N-heteroaromatic molecules exist in the lactam (oxo) form. It was, therefore, somewhat surprising to find substantial differences between the uv spectra of the neutral forms of 1-methyl derivatives **2b** and **2c** on the one hand and those of **2a** and **2d** on the other; the latter should have a proton at N-1 in the neutral form. A more detailed examination of the spectra was undertaken in order to understand this anomaly.

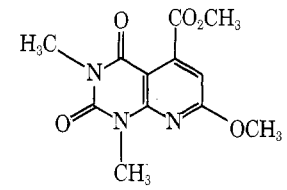
Determination of the pK_a values for **2a** and **2d** revealed no significant differences for either the first or second ionizations, suggesting that the first ionization in all four compounds occurs from N-8. As noted above, the spectra of the monoanions of the two 1-methyl derivatives **2b** and **2c** are virtually identical, as are those of **2a** and **2d.** One might suggest, therefore, that the spectral differences between the two pairs arise from initial ionization of N-1 from **2a** and **2d.** This possibility was excluded, however, by examination of the dianion spectra (Figure 1) in which the dianion of **2a** much more closely resembles that of the 1-methyl derivative **2b** than that of the 3-methyl derivative **2d.**

The most likely alternative explanation for the spectral difference is a difference in tautomeric structure of the 7-oxo (hydroxy) function in **2a, 2d** vs. **2b, 2c.** Two additional compounds were synthesized; 5-carbomethoxy-8-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**15**) was made from the reaction of 6-methylaminouracil and DMAD and 5-carbomethoxy-7-methoxy-1,3-dimethyl-2,4-dioxopyrido[2,3-





15



16

d]pyrimidine (**16**) was prepared by the methylation of **2c** with diazomethane. Compound **16** was shown to be an *O*-methyl rather than an *N*-methyl derivative by its ^{1}H NMR spectrum; the newly formed *O*-methyl substituent resonated at δ 3.97 vs. δ 3.53 for the 8-*N*-methyl derivative. The proton signal for C-6 of **16** appeared at δ 6.70, downfield 0.53 ppm from the C-6 H of **15**, as would be expected from the increase in ring current resulting from the "aromatization" of the system. Final confirmation of the structure was obtained by the conversion of **2c** to the 7-chloro derivative **17** with $POCl_3$–PCl_5. Reaction of **17** with methoxide gave **16**. That chlorination had occurred at the 7 position was confirmed by the catalytic dehalogenation of **17** to give 5-carbomethoxy-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (**18**); the presence in the ^{1}H NMR spectrum of a pair of doublets ($J_{6,7}$ = 4.8 Hz) is compatible only with **18**.[9]

Comparison of the uv spectra (Figure 2) of these "locked" lactam and lactim (**16**) tautomers with those of representative derivatives **2a** (unmethylated) and **2c** (1,3-dimethyl) suggests strongly that the influence of a methyl group at N-1 is to increase the proportion of lactim (hydroxy) tautomer of the C-7:N-8 tautomeric function. Such a finding suggests that a note of caution is in order in the frequently made assumption that substitution of O=CNCH$_3$ for O=CNH– in heteroaromatic system will have no effect on the uv spectrum.

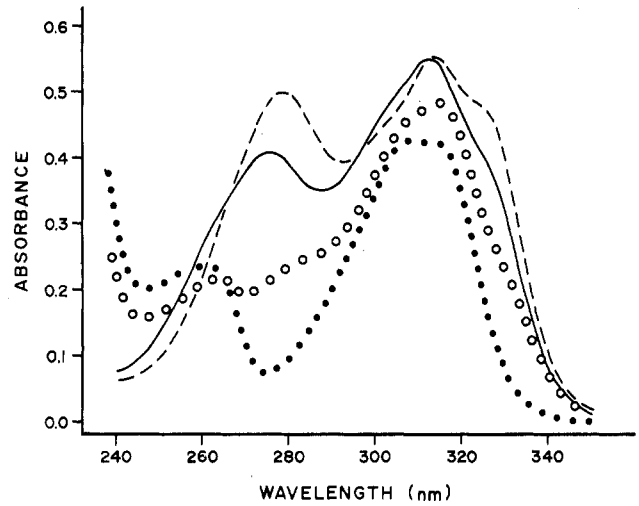


Figure 2. Uv spectra of neutral molecule of **2a** (—), **2c** (○), **15** (---), and **16** (●).

Experimental Section

^{1}H NMR spectra were obtained on a Jeolco C-60H spectrometer using $(CD_3)_2SO$ as a solvent with DSS as an internal standard. Uv spectra were run on a Cary 15 spectrophotometer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. pK_a values were determined spectrophotometrically according to Albert.[11]

5-Carbomethoxy-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (2a). Compound **1a** (640 mg, 5 mmol) was refluxed with DMAD (900 mg, 6 mmol) in H_2O (30 ml) for 4 h. The suspension was filtered hot to give 626 mg (52%) of **2a**. Recrystallization twice from DMF–2H_2O afforded 188 mg: mp 320 °C dec; uv (pH 1) 312 nm (ϵ 13 060), 275 (9750), (pH 7) 322 (14 430), 279 (9980), (pH 14) 324 (14 280), 270 (7070); ^{1}H NMR δ 11.27 (s, 1, NH), 6.35 (s, 1, CH), 3.87 (s, 3, OCH$_3$); pK_{a1} = 4.5 ± 1, pK_{a2} = 10.9 ± 1.

Anal. Calcd for $C_9H_7N_3O_5$: C, 45.57; H, 2.95; N, 17.72. Found: C, 45.55; H, 2.95; N, 17.76.

5-Carbomethoxy-1-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (2b). Compound **1b** (700 mg, 5 mmol) was refluxed with DMAD (900 mg, 6 mmol) in H_2O (30 ml) for 50 min. The clear yellow-orange solution was cooled to room temperature to give a heavy precipitate which was filtered and recrystallized from EtOH–H_2O (1:1) to yield 600 mg of pure product. Additional product (200 mg) was obtained from the filtrate. Total product, 800 mg (64%), was dissolved in hot EtOH, treated with charcoal, filtered, and evaporated to give 477 mg (38%) of **2b**: mp 289 °C dec; uv (pH 1) 314 nm (ϵ 12 050), 283 (sh), 263 (6980), (pH 7) 322 (16 200), 312 (16 300), 275 (8740), (pH 14) 328 (13 400), 275 (8600), 253 (12 000); ^{1}H NMR δ 11.50 (s, 1, NH), 6.45 (s, 1, CH), 3.85 (s, 3, OCH$_3$), 3.45 (s, 3, NCH$_3$); pK_{a1} = 4.6 ± 0.1, pK_{a2} = 11.3 ± 0.1.

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.59; N, 16.73. Found: C, 47.57; H, 3.55; N, 17.11.

5-Carbomethoxy-1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (2c). Compound **1c** (1.55 g, 10 mmol) was refluxed with DMAD (1.56 g, 11 mmol) in MeOH (50 ml) for 26 h. The reaction mixture was filtered hot, and the filtrate condensed to a small volume. The solid was filtered and recrystallized from MeOH to give 1.69 g (64%) of **2c**: mp 239–240 °C;[12] uv (pH 1) 315 nm (ϵ 14 100), 278 (9750), 262 (11 100), (pH 7) 323 (19 200), 313 (19 300), 273 (12 000), (pH 11) 322 (19 200), 312 (19 300), 273 (11 900); ^{1}H NMR δ 6.47 (s, 1, CH), 3.85 (s, 3, OCH$_3$), 3.48 (s, 3, NCH$_3$), 3.23 (s, 3, NCH$_3$); pK_{a1} = 4.6 ± 0.1, pK_{a2} = 11.3 ± 0.1.

Anal. Calcd for $C_{11}H_{11}N_3O_5$: C, 49.81; H, 4.18; N, 15.84. Found: C, 49.75; H, 4.15; N, 15.89.

5-Carbomethoxy-3-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (2d). Compound **1d** (705 mg, 5 mmol) was refluxed with DMAD (740 mg, 5.2 mmol) in H_2O (40 ml) for 3 h. The precipitate which formed was filtered to give a pink powder, which was dissolved in hot DMF–H_2O and treated with charcoal twice, and the filtrate was cooled to room temperature. The white crystals were filtered to give 546 mg (44%) of **2d**: mp 317–319 °C dec; uv (pH 1) 313 nm (ϵ 14 100), 275 (8300), (pH 7) 323 (15 300), 297 (9100), (pH 14) 326 (15 600), 268 (5700), 245 (13 000); ^{1}H NMR δ 6.40 (s, 1, CH), 3.73 (s, 3, OCH$_3$), 3.25 (s, 3, NCH$_3$); pK_a = 4.5 ± 0.1.

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.59; N, 16.73. Found: C, 48.03; H, 3.53; N, 16.52.

6-Carbethoxy-1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (9). Method A. Compound **8**[8] (550 mg, 3 mmol), piperidine (0.25 ml, 2.5 mmol), and diethyl malonate (1.5, 9.9 mmol) were refluxed in EtOH (20 ml) for 24 h. Diethyl malonate (1.0 ml, 6.6 mmol) was added and refluxing was continued for 48 h. The precipitate which formed on cooling was filtered to give 320 mg (42%) of white crystals. Recrystallization from dilute HCl (pH 2), then H_2O gave analytically pure sample: mp 196–170 °C; uv (pH 1) 317 nm (ϵ 21 200), 276 (14 300), (pH 7) 331 (25 100), 283 (18 200), (pH 11) 331 (24 700), 283 (17 800); ^{1}H NMR δ 8.33 (s, 1, CH), 4.27 (q, 2, CH$_2$), 3.43 (s, 3, NCH$_3$), 3.22 (s, 3, NCH$_3$), 1.33 (t, 3, CH$_3$).

Anal. Calcd for $C_{12}H_{13}N_3O_5$·0.5H_2O: C, 49.95; H, 4.85; N, 14.58. Found: C, 50.05; H, 5.19; N, 14.47.

Method B. Compounds **1c** (1.55 g, 10 mmol) and **5** (2.35 g, 11 mmol) were fused at an oil bath temperature of 210 °C. After cooling to room temperature, the melt was dissolved in 200 ml of $CHCl_3$, treated with charcoal, and filtered. The filtrate was reduced to a volume of 20 ml and the product precipitated by the addition of EtOH (200 ml). The solid was filtered and recrystallized from $CHCl_3$–MeOH to give 0.80 g (29%) of **9**: melting point, uv, ^{1}H NMR, and TLC were identical with those of compound prepared by method A.

Anal. Calcd for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.66; N, 15.05. Found: C, 51.52; H, 4.66; H, 14.94.

1,3-Dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (10). Method A. Compound **2c** (5 g, 19 mmol) was refluxed in H_2O (50 ml) containing NaOH (1.5 g, 37.5 mmol) for 8 h. The cooled reaction mixture was neutralized with dilute HCl. The precipitate was filtered and washed with H_2O to give 4 g (85%) of 1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-5-carboxylic acid: mp 320 °C; uv (pH 1) 312 nm (ϵ 12 400), 281 (sh), 263 (5980), (pH 7) 316 (17 700), 307 (18 000), 274 (7720), (pH 11) 316 (18 200), 307 (18 300), 274 (7720); ^{1}H NMR δ 6.47 (s, 1, CH), 3.53 (s, 3, NCH$_3$), 3.28 (s, 3, NCH$_3$).

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.59; N, 16.73. Found: C, 47.99; H, 3.69: N, 16.68.

This acid (4 g, 15.9 mmol) was heated at 330–350 °C in a vacuum sublimator for 2 h. The sublimate was triturated with EtOAc

and filtered. The filtered product was triturated with MeOH, filtered, and dried to give 216 mg (7%) of **10:** mp 274–275 °C; uv (pH 1) 311 nm (ε 13 750), 306 (sh), 281 (sh), 265 (sh), (pH 7) 321 (18 250); 308 (20 140), 274 (7700), (pH 11) 321 (18 670), 308 (20 350), 274 (7760); ^{1}H NMR δ 7.93 (d, 1, C-5 H, $J_{5,6}$ = 8.1 Hz), 6.42 (d, 1, C-6 H, $J_{5,6}$ = 8.1 Hz), 3.45 (s, 3, NCH_3), 3.21 (s, 3, NCH_3).

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.08; H, 4.43; H, 20.05.

Method B. Compounds **9** (3.5 g, 12.5 mmol) was refluxed in H_2O (50 ml) containing NaOH (1.5 g, 37.5 mmol) for 8 h. The solution was filtered and the filtrate was neutralized with dilute HCl to pH 7. The fine crystals which formed were filtered and triturated with methanol and with water to yield 3 g (94%) of 1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-6-carboxylic acid: mp > 320 °C; ^{1}H NMR δ 8.32 (s, 1, CH), 3.42 (s, 3, NCH_3), 3.22 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.59; N, 16.73. Found: C, 47.78; H, 3.60; N, 16.59.

This acid (2 g, 8.0 mmol) was treated as in method A to give 60 mg (4%) of **10,** identical by TLC, uv, ^{1}H NMR, and melting point with **10** from method A.

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.12; N, 4.37; N, 20.19.

Method C. Compound **1c** (455 mg, 3 mmol) and ethyl propiolate (0.40 ml, 4 mmol) were refluxed in H_2O (20 ml) for 24 h. The suspension was cooled and filtered to give 427 mg (69%) of **10.** Recrystallization from MeOH gave **10** identical by TLC, uv, ^{1}H NMR, and melting point with **10** from method A.

Dimethyl-2-(6-amino-2,4-dioxo-5-pyrimidinyl)fumaric Acid (12). Compound **1a** (640 mg, 5 mmol) and DMAD (900 mg, 6 mmol) were stirred in MeOH for 5 days. The filtrate was evaporated to dryness with EtOH twice, then triturated thoroughly with Et_2O and filtered to give 555 mg (41%) of **12.** For analysis, the solid was dissolved in EtOH, treated with charcoal, and filtered, and the filtrate allowed to stand at room temperature for several days. The crystals were filtered, washed with EtOH and dried: mp 225 °C dec; uv (pH 1) 312 nm (ε 11 400), 269 (11 100), (pH 7) 322 (14 500), 279 (10 000), (pH 11) 322 (14 500), 273 (8340), 228 (17 200); ^{1}H NMR δ 10.37 (s, 1, NH), 10.22 (s, 1, NH), 6.65 (s, 1, CH), 6.22 (s, 2, NH_2), 3.68 (s, 3, OCH_3), 3.65 (s, 3, OCH_3).

Anal. Calcd for $C_{10}H_{11}N_3O_6 \cdot 0.5H_2O$: C, 43.15; H, 4.35; N, 15.11. Found: C, 43.23; H, 4.40; N, 15.19.

Conversion of 12 to 2a. **12** (40 mg) was heated in DMF at 150 °C for 30 min. Evaporation of DMF gave only a compound identical by tlc and ^{1}H NMR with **2a.**

6-Amino-5-(3-carbomethoxy-2-propynoyl)uracil (13) and Dimethyl-2-(6-amino-2,4-dioxo-5-pyrimidinyl)maleic Acid (14). Compound **1a** (1.0 g, 7.87 mmol) was dissolved in Me_2SO (15 ml). DMAD (1.16 g, 8.13 mmol) was added and the solution stirred overnight. MeOH (75 ml) was added and the solution stored at 5 °C for 24 h. The yellow crystals were filtered to give 113 mg of **13** (5.8%). To the filtrate was added 400 ml of Et_2O and the yellow solution stored at 5 °C for 2 days. Filtration afforded 918 mg (40.8%) of **14.** For analysis **13** was recrystallized from DMF–H_2O: mp <310 °C (slowly darkens); uv (pH 1) 427 nm (ε 9200), 276 (14 400), 262 (sh), (pH 7) 333 (23 500), 273 (10 000), (pH 11) 333 (24 700), 273 (9300); ^{1}H NMR δ 10.08 (br, 4, NH_2, NH, NH), 3.75 (s, 3, CH_3).

Anal. Calcd for $C_9H_7N_3O_5 \cdot 0.5H_2O$: C, 43.90; H, 3.25; N, 17.07. Found: C, 43.99; H, 3.31; N, 16.99.

Recrystallization of **14** by dissolving in 350 ml of MeOH at 25 °C, followed by evaporation in vacuo to ~100 ml and then addition of 200 ml of Et_2O, gave 636 mg (28%) of pure compound: mp 195 °C effervescence (slowly decomposed); uv (pH 1) 328 nm (ε 7400), 267 (14 400), (pH 7) 338 (6400), 267 (12 900), (pH 11) 388 (4700), 271 (16 500); ^{1}H NMR δ 10.55 (s, 1, NH), 10.30 (s, 1, NH), 6.65 (s, 2, NH_2), 5.95 (s, 1, CH), 3.65 (s, 6, OCH_3).

Anal. Calcd for $C_{10}H_{11}N_3O_6 \cdot H_2O$: C, 41.81; H, 4.53; N, 14.63. Found: C, 41.84; H, 4.72; N, 14.96.

5-Carbomethoxy-8-methyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine (15). DMAD (575 mg, 4 mmol) and 6-methylaminouracil[13] (423 mg, 3 mmol) were refluxed in H_2O (30 ml) for 1 h. The hot solution was filtered through charcoal and the filtrate cooled overnight to give 261 mg (35%) of **15** after filtration. An analytical sample was recrystallized from EtOH–H_2O which decomposed at >305 °C: uv (pH 1) 313 nm (ε 13 300), 279 (12 050), (pH 7) 335 (14 900), 284 (11 100), (pH 14) 345 (18 000), 279 (14 600), 253 (12 000); ^{1}H NMR δ 11.50 (s, 1, NH), 6.17 (s, 1, CH), 3.83 (s, 3, OCH_3), 3.53 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.61; N, 16.72. Found: C, 47.89; H, 3.84; N, 16.44.

5-Carbomethoxy-7-methoxy-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (16). Method A. Compound **2c** (500 mg, 1.9 mmol) was dissolved in methanol (75 ml) with stirring. To the clear solution was added 40 ml of diazomethane–ether solution portionwise until the yellow color was maintained for 1 h. After evaporation in vacuo, the residue was recrystallized from EtOH to give 450 mg (86%) of **16:** mp 154–155 °C; uv (pH 1) 307 nm (br) (ε 11 800), 261 (7300), (pH 7) 207 (br) (12 000), 261 (7200), (pH 11) 307 (br) (12 000), 261 (7300); ^{1}H NMR δ 6.70 (s, 1, CH), 3.97 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 3.50 (s, 3, NCH_3), 3.20 (s, 3, NCH_3).

Anal. Calcd for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.66; N, 15.05. Found: C, 51.67; H, 4.81; N, 15.25.

Method B. To MeOH (3 ml) containing Na (70 mg) was added **17** (100 mg, 0.35 mmol). After stirring for 1 h, H_2O (2 ml) was added and the pH adjusted to 7 with HOAc. Filtration afforded 85 mg (86%) of **16,** identical by TLC, uv, ^{1}H NMR, and melting point with **16** from method A.

5-Carbomethoxy-7-chloro-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (17). Compound **2c** (2.65 g, 10 mmol) was refluxed in $POCl_3$ (50 ml) containing PCl_5 (2.3 g, 11 mmol) for 3 h. Excess $POCl_3$ was removed in vacuo, and the residue was stirred with 150 g of ice for 15 min, then extracted with $CHCl_3$ (3 × 125 ml). The $CHCl_3$ was extracted with ice–H_2O three times and dried over $MgSO_4$. This was evaporated to about 10 ml, 50 ml of petroleum ether was added, and the solid was filtered. The filtrate was evaporated and triturated with ether to give a white solid (937 mg) of nearly pure **17.** The product was used for the synthesis of **16** and **18** without further purification: ^{1}H NMR δ 7.52 (s, 1, CH), 3.87 (s, 3, OCH_3), 3.50 (s, 3, NCH_3), 3.25 (s, 3, NCH_3).

5-Carbomethoxy-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine (18). Compound **17** (500 mg, 1.76 mmol) was dissolved in 1,2-dimethoxyethane (100 ml) in which Pd/C 10% (200 mg) and NaOAc (145 mg, 3.5 mmol) were suspended. This was shaken under H_2 (42 psi) for 36 h. Filtration through Celite, followed by evaporation in vacuo, gave an oily solid which was dissolved in boiling EtOH (20 ml). Cooling to room temperature gave 246 mg of **18** (56%): mp 153–155 °C; uv (pH 1) 315 nm (ε 6300), 248 (sh), (pH 7) 315 (6700), 248 (sh), (pH 11) 315 (6100), 248 (sh); ^{1}H NMR δ 8.70 (d, 1, C_7 H), 7.23 (d, 1, C_6 H) ($J_{6,7}$ = 4.8 Hz), 3.82 (s, 3, OCH_3), 3.50 (s, 3, NCH_3), 3.22 (s, 3, NCH_3).

Anal. Calcd for $C_{11}H_{11}N_3O_4 \cdot 0.5H_2O$: C, 51.16; H, 4.68; N, 16.30. Found: C, 51.05; H, 4.68; N, 16.37.

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Registry No.—**1a,** 873-83-6; **1b,** 2434-53-9; **1c,** 6642-31-5; **1d,** 21236-97-5; **2a,** 57821-16-6; **2b,** 57821-17-7; **2c,** 37587-38-5; **2d,** 57821-18-8; **5,** 87-13-8; **8,** 54660-80-9; **9,** 57821-19-9; **10,** 57821-20-2; **12,** 57821-21-3; **13,** 57821-22-4; **14,** 57821-23-5; **15,** 57821-24-6; **16,** 57821-25-7; **17,** 57821-26-8; **18,** 57821-27-9; DMAD, 762-42-5; diethyl malonate, 105-53-3; 1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-5-carboxylic acid, 57821-28-0; 1,3-dimethyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-6-carboxylic acid, 57842-79-2; ethyl propiolate, 623-47-2; 6-methylaminouracil, 34284-87-2; diazomethane, 334-88-3; MeOH, 67-56-1.

References and Notes

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