Pyrimidines. 21. Novel Reactions of 5-Cyano-1,3-dimethyluracil with Carbon Nucleophiles. A Facile Preparation of Certain Pyrido[2,3-*d*]pyrimidines [1]

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Treatment of 5-cyano-1,3-dimethyluracil (**8**) with an activated acetonitrile, such as malononitrile, ethyl cyanoacetate or cyanoacetamide, in base afforded 7-amino-6-cyano-, 7-amino-6-ethoxycarbonyl-, and 7-amino-6-aminocarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**18b**, **18c** and **18d**, respectively) in high yields. On the other hand, reaction of **8** with acetonitrile in base gave the Michael adduct, 5-cyano-6-cyanomethyl-5,6-dihydrouracil (**15**, R = H), and the hydrated product, 1,3-dimethyluracil-5-carboxamide (**9**) as the major products, and 7-amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**18a**) in only very low yield. Similar reaction with butanone gave 7-ethyl-1,3-dimethyl- and 1,3,6,7-tetramethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**10b** and **10c**) in low yields.

When **8** was treated with diethylmalonate in base, only a small amount of 6-ethoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**19**) was obtained together with 1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**20**) and **18c** (also in low yields). Treatment of **8** in ethanolic sodium ethoxide without added carbon nucleophile gave significant amounts (14%) of **20** and a small amount of **18c**.

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The pyrido[2,3-*d*]pyrimidine ring system is found in a number of biologically active compounds [2], including antitumor [3], antibacterial [4], antimalarial [5], antihypertensive [6], antiallergic [7], antiphlogistic [8], analgesic [8], and anticonvulsive [8] substances. During the course of our studies on heterocyclic ring transformations we discovered a novel, high-yielding one-step procedure for the preparation of this ring system, which is described in this article [9].

The urea portion of 1,3-dimethyluracil derivatives **1** has

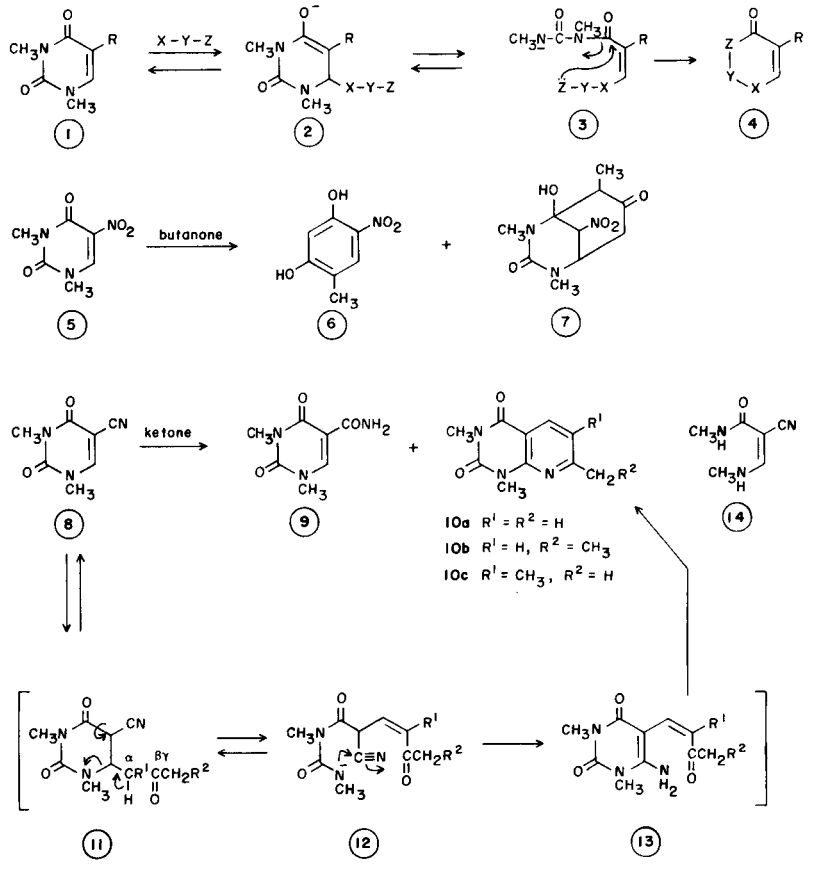
Table 1

Spectral Characteristics of Certain Pyrido[2,3-*d*]pyrimidines

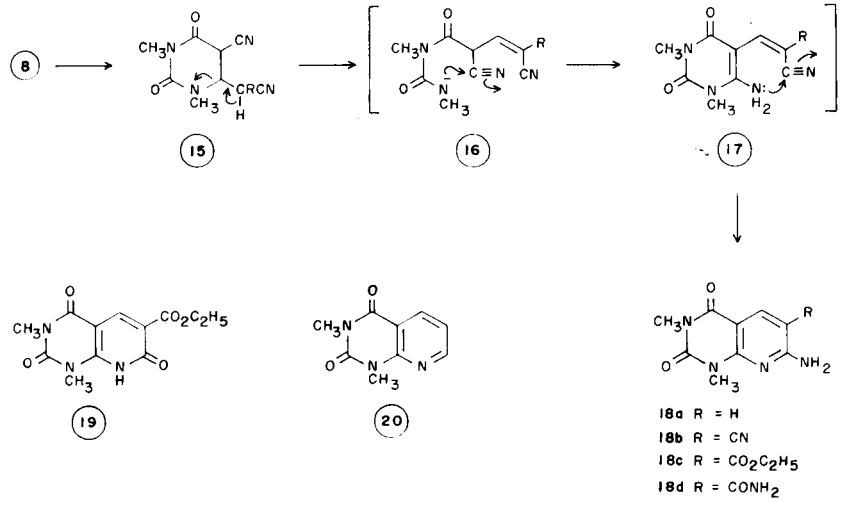
Compound	UV (water) λ max	ε max	λ min	ε min	PMR parameters Chemical Shifts (δ)
10a	308 [a]	8700	266	1100	8.32 (d, H-5) [b] 7.04 (d, H-6), 3.71 (s, NMe), 3.48 (s,
	248 sh	6400			NMe), 2.62 (s, 7-Me) [c]
10b	309	9900	267	1100	8.34 (d, H-5) [b], 7.06 (d, H-6), 3.73 (s, NMe), 3.48 (s,
	249 sh	7100			NMe), 2.89 (q, C*H*$_2$Me), 1.35 (t, CH$_2$*Me*) [c]
10c	316	8600	269	930	8.13 (s, H-5), 3.71 (s, NMe), 3.47 (s, NMe), 2.56 (s,
	248	7600	242	7300	7-Me), 2.34 (s, 6-Me) [c]
18a	317	22100	287	11000	7.73 (brs, NH$_2$), 7.52 (d, H-5) [d], 6.50 (d, H-6), 3.33 (s,
	276	11100	243	1500	NMe), 3.13 (s, NMe) [e]
	220 sh	9600			
18b [f]	330	16200	298	3500	8.32 (s, H-5), 7.88 (brs, NH$_2$), 3.44 (s NMe), 3.23 (s,
	289	12400	262	5400	NMe) [e]
	242	12600			
18c	336	18400	298	3300	8.87 (s, H-5), 8.27 (brs, NH), 5.71 (brs, NH), 4.36 (q,
	286	15700	265	6800	C*H*$_2$Me), 3.60 (s, NMe), 3.43 (s, NMe), 1.40 (t,
	243	13000			CH$_2$*Me*) [e]
18d	332	7100	298	2250	8.58 (s, H-5), 8.25 (brs, NH$_2$), 3.47 (s, NMe), 3.25
	284	5710	264	2480	(s, NMe) [e]
	232	1430			
19	337 sh	11900	292	6400	12.53 (s, OH), 8.55 (s, H-5), 4.31 (q, C*H*$_2$Me), 3.48 (s,
	319	16900	255	5400	NMe), 3.25 (s, NMe), 1.32 (t, C*H*$_2$Me) [e]
	277	11800			
20	309	6400	264	780	8.67 (dd, H-7), 8.47 (dd, H-6), 8.47 (dd, H-5), 3.74 (s,
	245 sh	6900			NMe), 3.50 (s, NMe) [e,g]

[a] nm. [b] $J_{5,6}$ = 8.0 Hz. [c] In deuteriochloroform. [d] $J_{5,6}$ = 5.6 Hz. [e] In d_6-DMSO. [f] Ir (potassium bromide): 2220 cm^{-1} (CN). [g] $J_{5,6}$ = 7.8, $J_{5,7}$ = 1.8, $J_{6,7}$ = 4.9 Hz.

Scheme 1

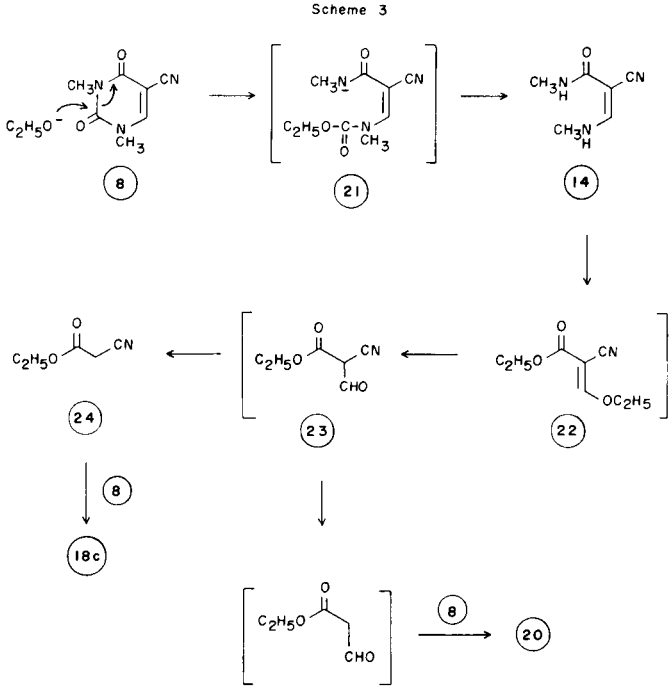


Scheme 2



been displaced by the N-C-N or C-C-N fragment of 1,3-ambident nucleophiles leading to new pyrimidine [10,11] or pyridine [12,13] derivatives. These ring transformations most probably proceed by the S_{RN}(ANRORC) mechanism [14] as delineated in Scheme 1, namely, the reaction would be initiated by addition of an ambident nucleophile (X-Y-Z) to form a Michael adduct **2** from which an open-chain intermediate **3** would be produced. Subsequent ring closure by attack of the second nucleophile in **3** on C4 with concomitant elimination of 1,3-dimethylurea would result

Scheme 3



in the formation of a new heterocyclic product **4**. When a ketone was used as the 1,3-ambident nucleophile in order to convert the pyrimidine into the benzene system, activation of the uracil ring by introduction of an electron-withdrawing group (*e.g.* NO_2) on C5 is necessary [15]. However, due probably to stabilization of the Michael adduct by formation of *aci*-nitronate salt in base, the pyrimidine to benzene ring transformation is not straightforward and other products (*e.g.* **7**) are formed [15] in addition to the substituted nitroresorcinol **6** from 1,3-dimethyl-5-nitrouracil (**5**).

In order to avoid the complications caused by a nitro function, we treated 5-cyano-1,3-dimethyluracil (**8**) with acetone in ethanolic sodium ethoxide [9]. Unexpectedly, the desired cyanoresorcinol was not obtained but two products, 1,3-dimethyluracil-5-carboxamide (**9**) [16] and 1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**10a**) [17] were obtained instead. The former arose from hydration of the nitrile in **8**. The latter product **10a** apparently was formed from the Michael adduct **11** which underwent ring-opening to give **12**. The regular S_N(ANRORC) mechanism, which would lead to the formation of 4-cyanoresorcinol by attack of the γ-carbon to C4 in **12** with concomitant elimination of 1,3-dimethylurea, did not operate in this case. Instead, ring-closure apparently occurred between the terminal urea nitrogen in **12** and the exocyclic cyano function giving rise to the 6-aminouracil intermediate **13**. Intramolecular condensation of the amino group in **13** with the neighboring ketone would then yield **10a**. Similar treatment of **8** with butanone afforded two bicyclic products, 7-ethyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**10b**) and 1,3,6,7-tetramethylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**10c**) in 21 and 2% yield, respectively. Apparently, attack on C6 of **8** by the less hindered carbon nucleophile occurred predominantly. In addition to **10b** and **10c**, **9** and *N,N'*-dimethyl-3-amino-2-cyanoacrylamide (**14**) were also isolated from the reaction mixture in 3% and 9% yield, respectively. The formation of **14** occurred apparently by attack of ethoxide on C2 of **8** to form a carbamate intermediate (Scheme 3) followed by decarboethoxylation. Base-catalyzed cleavage of the N2-C3 bond of pyrimidines is known to occur during certain intramolecular rearrangement of cytosine derivatives [18, 19]. Excision of the 2-carbonyl of uracil derivatives, however, is quite rare [20]. In order to confirm the formation of **14** from **8** in base, **8** was treated with sodium ethoxide for 1 hour at reflux. Three spots corresponding to **8**, **9** and **14** were detected on a tlc plate. From the reaction mixture, compounds **9** and **14** were isolated in pure crystalline form in yields of 18 and 17%, respectively, and 32% of **8** was recovered.

When acetonitrile was used as the ambident nucleophile instead of a ketone in the above reaction, a small amount (3%) of 7-amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**18a**) (Scheme 2) was obtained together with **9** (15%) and 5-cyano-6-cyanomethyl-5,6-dihydrouracil (**15**, R = H) (21%). A plausible mechanism for the formation of **18a** is shown in Scheme 2. Addition of acetonitrile across the 5,6-double bond of **8** affords **15**, (R = H). Base-catalyzed abstraction of the γ-proton in **15** would result in the formation of the open-chain intermediate **16** which would cyclize to the 6-aminouracil intermediate **17**. Intramolecular attack of the amino group on the cyano carbon in **17** would furnish the formation of **18a**.

The mechanism in Scheme 2 suggests that treatment of **8** with an activated acetonitrile should afford a bicyclic product more readily. The Michael adduct (**15**, R = electron withdrawing group) should be more susceptible to

Table 2

Analytical Data for **10**, **14**, **15**, **18**, **19** and **20**

Compound	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
10a	$C_{10}H_{11}N_3O_2$	58.53	5.40	20.48	58.40	5.38	20.32
10b	$C_{11}H_{13}N_3O_2$	60.26	5.98	19.17	60.40	6.05	19.34
10c	$C_{11}H_{13}N_3O_2$	60.26	5.98	19.17	60.11	6.09	19.21
14	$C_5H_9N_3O$	51.79	6.52	30.20	51.80	6.48	30.13
15	$C_9H_{10}N_4O_2$	52.42	4.89	27.17	52.40	5.00	27.21
18a	$C_9H_{10}N_4O_2 \cdot \frac{1}{4}H_2O$ [a]	51.31	4.90	26.59	51.13	4.85	26.50
18b	$C_{10}H_9N_5O_2$	51.95	3.92	30.29	51.80	4.03	30.03
18c	$C_{12}H_{14}N_4O_4$	51.80	5.07	20.13	51.88	5.04	20.20
18d	$C_{10}H_{11}N_5O_3$	48.32	4.51	28.15	48.18	4.45	28.10
19	$C_{12}H_{13}N_3O_5$	51.61	4.69	15.05	51.56	4.79	14.95
20	$C_9H_9N_3O_2$	56.54	4.74	21.98	56.77	4.86	22.03

[a] The presence of a small amount of water was detected by pmr.

ring opening to yield **16** since the α-proton is more acidic than in **15** (R = H). Cyclization of **16** to the 6-aminouracil intermediate **17** and subsequent formation of the bicyclic product **18** are also expected to occur readily. Indeed, when **8** was treated with malononitrile in ethanolic sodium ethoxide, 7-amino-6-cyano-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**18b**) was obtained in almost quantitative yield. Treatment of **8** with ethyl cyanoacetate or cyanoacetamide also gave the corresponding bicyclic products, 7-amino-6-ethoxycarbonyl-1,3-dimethylpyrido-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**18c**) and 7-amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-6-carboxamide (**18d**) in very high yields.

When diethyl malonate was employed as the nucleophile, the expected ethoxycarbonyl-1,3-dimethylpyrido-[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**19**) was obtained in only 4% yield along with 1,3-dimethylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**20**) (14%) and **18c** (3%). The formation of the latter two products **18c** and **20** was quite unexpected but could be explained. Compound **18c** can be formed readily by reaction of **8** with ethyl cyanoacetate (**24**) [9] (*vide supra*), and **20** by condensation of **8** with ethyl formylacetate (**25**) (Scheme 3). These reactants (**24** and **25**) may be derived from ethyl formylcyanoacetate (**23**) by deformylation to **24** or by hydrolysis of the cyano to carboxyl group followed by decarboxylation to **25**. Compound **23**, in turn, may arise from the enamine **14** *via* solvolysis as shown in Scheme 3. In order to substantiate the above mechanism, **8** was treated with ethanolic sodium ethoxide for 24 hours at reflux, and obtained substantial amount (13%) of **20** from the reaction mixture together with **9** (34%). A small amount of **18c** was detected but none of **14** (obtained in 17% yield after one hour treatment), apparently due to solvolysis to **22** during the prolonged treatment. These results are consistent with the mechanism of formation of **18c** and **20** from **8** as proposed in Scheme 3.

The method we have developed for the synthesis of **18b-d** in high yields from 5-cyano-1,3-dimethyluracil (**8**) may be applicable to the syntheses of other pyrido[2,3-*d*]-pyrimidines. Studies along this line are now in progress in our laboratory.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The pmr spectra were recorded on a JEOL PFT-100 spectrometer using tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (δ) and signals are described as s (singlet), d (doublet) t (triplet), q (quartet), dd (double doublet) and m (multiplet). Values given for coupling constants are first order. The uv absorption spectral data were obtained on a Cary Model-15 spectrometer. The tlc was performed on Uniplates purchased from Analtech Co., and column chromatography on silica gel G-60 (70-230 mesh, ASTM, Merck). Microanalyses were performed by M. H. W. Laboratories.

Reaction of **8** with Acetone.

A mixture of **8** (1.65 g, 10 mmoles) and acetone (10 ml) in ethanolic sodium ethoxide (freshly prepared by dissolving 460 mg of metallic sodium in 30 ml of ethanol) was heated under reflux for 2 hours. After cooling to room temperature, the mixture was neutralized with Dowex-50(H). The resin was filtered and washed with ethanol, and the combined filtrate and washings were concentrated *in vacuo* to a syrup which contained two major products as judged by tlc (chloroform-methanol 9:1 v/v) was chromatographed over a column of silica gel (40 × 3 cm). One of the products, eluted with chloroform and crystallized from petroleum-ether and ether, was 1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**10a**), 360 mg (18%), mp 155-156° (lit [17] mp 157.6-159°). For spectral and analytical data, see Tables 1 and 2.

The second product, eluted with chloroform-methanol (30:1 v/v) and crystallized from ethanol, was 1,3-dimethyluracil-5-carboxamide (**9**), mp 215-216° (lit [16] mp 216-218°).

Reaction of **8** with Butanone.

A mixture of **8** (3.30 g, 20 mmoles) and butanone (20 ml) in freshly prepared ethanolic sodium ethoxide (by dissolving 920 mg of metallic sodium in 50 ml of ethanol) was heated under reflux for 2 hours. After neutralization of the mixture with Dowex-50(H), the resin was filtered and washed with ethanol. The combined filtrate and washings were concentrated *in vacuo* to a syrup, which was dissolved in a mixture of chloroform and methanol (30:1 v/v) (10 ml). Silica gel (5 g) was added to the solution and the mixture was concentrated *in vacuo*. The residue was placed on the top of a silica gel column (40 × 3 cm). Elution of the column with chloroform afforded two uv absorbing fractions. The first fraction was concentrated *in vacuo* and the residue was crystallized from *n*-hexane-ether (1:1) to give 7-ethyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**10b**), 854 mg (21%), mp 83-84°.

The mother liquor of crystallization was evaporated *in vacuo* and the residue crystallized from ether-petroleum ether to afford 1,3,6,7-tetramethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**10c**), 58 mg (1.4%), mp 147-148°. The spectral and analytical data of these compounds are given in Tables 1 and 2.

The second uv absorbing fraction was concentrated and the residue crystallized from chloroform-ether. *N*,*N'*-Dimethyl-3-amino-2-cyanoacrylamide (**14**) (243 mg, 8.7%) was obtained as colorless crystals, mp 134-135°; pmr (deuteriochloroform): δ 9.46 (1H, d, NH), 7.13 (1H, d, H2, collapsed to a singlet upon addition of deuterium oxide), 5.81 (1H, d, NH), 3.07 (3H, d, NMe, collapsed to a singlet upon addition of deuterium oxide), 2.84 (3H, d, NMe, became a singlet upon addition of deuterium oxide); ir (potassium bromide): 2210 cm^{-1} (CN). See Table 2 for analytical data.

Reaction of **8** with Acetonitrile.

A mixture of **8** (1.65 g, 10 mmoles) and acetonitrile (10 ml) in freshly prepared ethanolic sodium ethoxide (920 mg of metallic sodium in 50 ml of ethanol) was heated at reflux for 20 hours. After cooling to room temperature, insoluble precipitates were filtered and the filtrate was concentrated to about 10 ml. After standing overnight, 5-cyano-6-cyanomethyl-5,6-dihydrouracil (**15**, R = H) crystallized was collected by filtration and recrystallized from ethanol to give an analytically pure sample, 436 mg (21%), mp 174-175°; pmr (d_6-pyridine): δ 5.76 (1H, m, H6 became a singlet upon addition of deuterium oxide), 4.87 (1H, m, H-5, exchangeable), 3.49 (2H, m, exocyclic methylene, exchangeable), 3.35 (3H, s, NMe), 3.26 (3H, s, NMe).

The mother liquors were combined, evaporated *in vacuo*, and the residue was crystallized from chloroform-methanol to afford 7-amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**18a**). After two recrystallizations from the same solvent system, an analytical sample of **18a** (65 mg, 3.2%) was obtained, mp 324-325°.

The insoluble precipitates filtered from the reaction mixture were dissolved in water (20 ml) and the solution acidified to *p*H ~ 2 with 2*N* hydrochloric acid, and the solution was extracted with chloroform (4 × 50 ml). The combined extracts were dried over sodium sulfate, concentra-

ted to dryness *in vacuo*, and the residue was crystallized from ethanol to afford 274 mg (15%) of **9** which was identical in all respects with an authentic sample.

The spectral and analytical data for **15** and **18** are listed in Tables 1 and 2.

7-Amino-6-cyano-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**18b**).

A mixture of **8** (1.65 g, 10 mmoles) and malononitrile (66 mg, 10 mmoles) in freshly prepared ethanolic sodium ethoxide (460 mg of metallic sodium in 60 ml of ethanol) was heated at reflux for 20 minutes. After cooling the mixture to room temperature, crystalline precipitates were collected by filtration and recrystallized from a mixture of *N,N*-dimethylformamide and ethanol to give 2.08 g (90%) of **18b**, mp 352-353° (lit [21] mp 354°). See Tables 1 and 2 for spectral and analytical data for **18b**.

7-Amino-6-ethoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**18c**).

Reaction of **8** (1.65 g, 10 mmoles) with ethyl cyanoacetate (1.70 g, 15 mmoles) in refluxing ethanolic sodium ethoxide (prepared by dissolving 460 mg of metallic sodium in 60 ml of ethanol) for 20 minutes affording precipitates which, after recrystallization from chloroform-methanol, afforded 2.53 g of **18c**, mp 213-214°. Additional 231 mg of **18c** was obtained from the mother liquor (total yield, 99%). See Tables 1 and 2 for spectral and analytical data for **18c**.

7-Amino-6-aminocarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**18d**).

Treatment of a mixture of **8** (1.69 g, 10 mmoles) and cyanoacetamide (0.70 g, 10 mmoles) in ethanolic sodium ethoxide (prepared from 460 mg of sodium and 60 ml of ethanol) at reflux for 20 minutes afforded 200 mg (80%) of **18d** after recrystallization from methanol-*N,N*-dimethylformamide, mp 350°. Spectral and analytical data for **18d** are reported in Tables 1 and 2.

Reaction of **8** with Diethyl Malonate.

A mixture of **8** (1.65 g, 10 mmoles) and diethyl malonate (2.4 g, 15 mmoles) in ethanolic sodium ethoxide (freshly prepared by dissolving 690 mg of metallic sodium in 80 ml of ethanol) was heated at reflux for 20 hours. After neutralization of the mixture with Dowex 50(H), the resin was filtered and washed with ethanol. The combined filtrate and washings were concentrated *in vacuo* to dryness and the residue which contained three major products (tlc, *n*-hexane-ethyl acetate 4:1 v/v, developed twice) was chromatographed over a silica gel column (40 × 5 cm) using *n*-hexane-ethyl acetate (5:1) as the eluent. 1,3-Dimethylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**20**, 264 mg, 14%) (recrystallized from chloroform-methanol) was eluted first followed by 6-ethoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**19**, 87 mg, 3.1%, after recrystallization from chloroform-methanol).

The third product was eluted from the column with *n*-hexane-ethyl acetate (4:1) (87 mg, 3.1%) which was identical with **18c** prepared by condensation of **8** with ethyl cyanoacetate.

The spectral and analytical data for **19** and **20** are reported in Tables 1 and 2.

Reaction of **8** with Sodium Ethoxide.

(a) A mixture of **8** (258 mg, 1.65 mmoles) and ethanolic sodium ethoxide (freshly prepared from 76 mg of sodium and 20 ml of ethanol) was heated at reflux for 1 hour. After cooling to room temperature, the mixture was neutralized [Dowex-50(H)], concentrated *in vacuo*, and the residue which showed three major spots on tlc (chloroform-methanol 10:1 v/v) corresponding to **8**, **9** and **14** was chromatographed over a silica gel column (20 × 2 cm). Compound **14** was eluted first with chloroform, and was crystallized from chloroform-ether (37 mg, 17%), mp 134-135°, unchanged on admixture with an authentic sample. From the second fraction, **8** (52 mg, 32%) was recovered. The third component, eluted from the column with chloroform-methanol (30:1 v/v) was identical with **9** [after recrystallization from ethanol, 21 mg (18%)], mp 215-216°. A mixture mp with an authentic sample showed no depression.

(b) A solution of **8** (1.65 g, 10 mmoles) in ethanolic sodium ethoxide (prepared from 460 mg of sodium and 60 ml of ethanol) was heated at reflux for 24 hours. The mixture was cooled to room temperature, neutralized with Dowex 50(H), and the resin was filtered and washed with ethanol. The combined filtrate and washings were concentrated *in vacuo* to dryness. Te residue which contained four major components **8**, **9**, **18c** and **20** as judged by tlc (*n*-hexane-ethyl acetate 3:2) was chromatographed over a silica gel column (30 × 5 cm). Compounds **8** (108 mg, 6.6%) and **20** (246 mg, 14%) were eluted from the column with *n*-hexane-ethyl acetate (4:1). Compound **9** (622 mg, 34%) was eluted with *n*-hexane-ethyl acetate (3:2). Compound **18c** was not isolated in a pure state although its presence was detected by tlc.

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