Further Study on 1,3-Dialkylaminouracil with Dimethyl Acetylenedicarboxylate

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On the treatment of 1,3-dialkyl-6-alkylaminouracil (**1**) with dimethyl acetylenedicarboxylate (DMAD), we were able to develop a new synthesis of deazapurine (pyrrolo[2,3-*d*]pyrimidine, **4**), and proposed the plausible mechanism for the formation of **3** and **4** from the adduct [dimethyl 2-(1,3-dialkyl-6-alkylamino-2,4-dioxopyrimidin-5-yl)fumarate, **2**] of **1** with DMAD.

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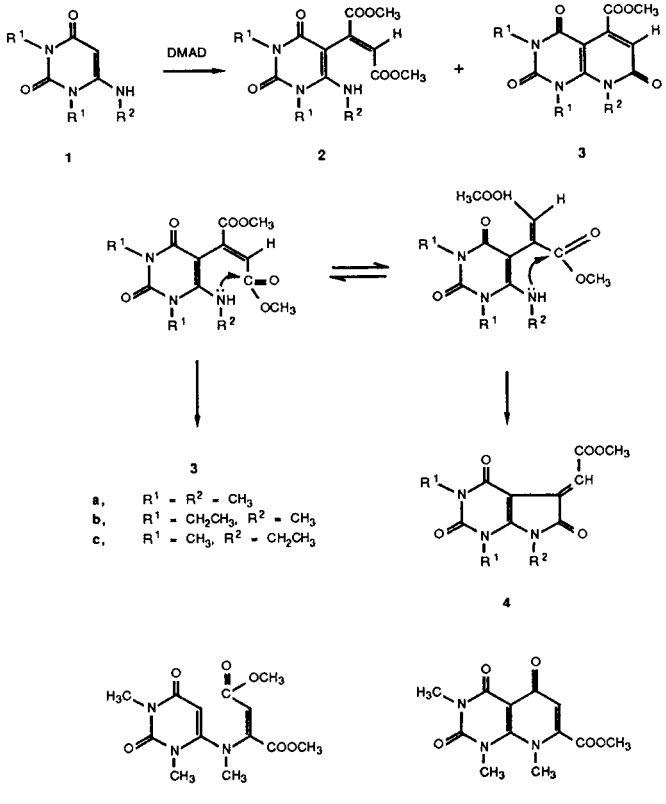
In a preceding paper of this series, we reported a new and convenient synthetic procedure of 1,3-dialkylpyrido-[2,3-*d*]pyrimidines [1] and substituted pyrrolo- and furopyrimidines [2]. Previously it was reported [3] that a reaction of **1** (R^1 = Me, R^2 = H) with DMAD gave a mixture of a pair of isomeric products to which were given the pyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**3**) and -2,4,5(1*H*,3*H*,8*H*)-trione (**6**) structures on the assumption that the reaction would proceed through formation of two intermediates, **2** and **5**. We describe herein that the supposed structure of **6** should be revised as compound **4** and clarified the mechanism for the formation of **3** and **4**.

Treatment of 1,3-dimethyl-6-methylaminouracil (**1a**) with DMAD in methanol at room temperature afforded dimethyl 2-(1,3-dimethyl-6-methylamino-2,4-dioxopyrimidin-5-yl)fumarate (**2a**), together with a small amount of 1,3,8-trimethyl-5-methoxycarbonylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**3a**) [3] in 37% and 7.5% yields, respectively. The ^{1}H-nmr, uv, mass spectral data and elemental analysis were consistent with the indicated structures of **2a** and **3a**.

Similarly, dimethyl 2-(1,3-dialkyl-6-alkylamino-2,4-dioxopyrimidin-5-yl)fumarate (**2b**, 39%; **2c**, 29%) and 1,3-dialkyl-5-methoxycarbonyl-8-alkylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**3b**, 5.3%; **3c**, 1.6%) were obtained by treatment of **1b** and **1c** with DMAD in methanol in fair or poor yields, respectively. The ^{1}H-nmr and mass spectral data for **3b** and **3c** are also consistent with their structures. Assignment of the 5-substituted uracil structure **2** for the major product is made on the basis of the ^{1}H-nmr spectroscopy which showed that this compound contains two methoxycarbonyl groups and NH function in its molecule.

The adduct **2a** of **1a** with DMAD was refluxed in methanol for 30 minutes to give a 4:1 mixture of two isomers **3a** and **4a** of which the major product was the known pyridopyrimidine **3a** [3].

Under drastic conditions of heating at 165-175° in an oil bath for 20 minutes, **2a** gave rise to a 4:1 mixture of **4a** and **3a**. In a similar manner, **2b** afforded an 85:15 mixture of **4b** and **3b**, and **2c** gave a readily separable 9:1 mixture of **4c** and **3c**. Thus, the formation of pyrrolopyrimidine **4** requires more drastic conditions than does pyridopyrimidine formation. This is expected since the five-membered ring in **4** is much more strained than the pyridone ring in **3**. In the Figure 1, the uv spectral pattern of **2a** and **3a** shows type-A and that of **2b**, **3b**, **4a** and **4b** shows type-B.



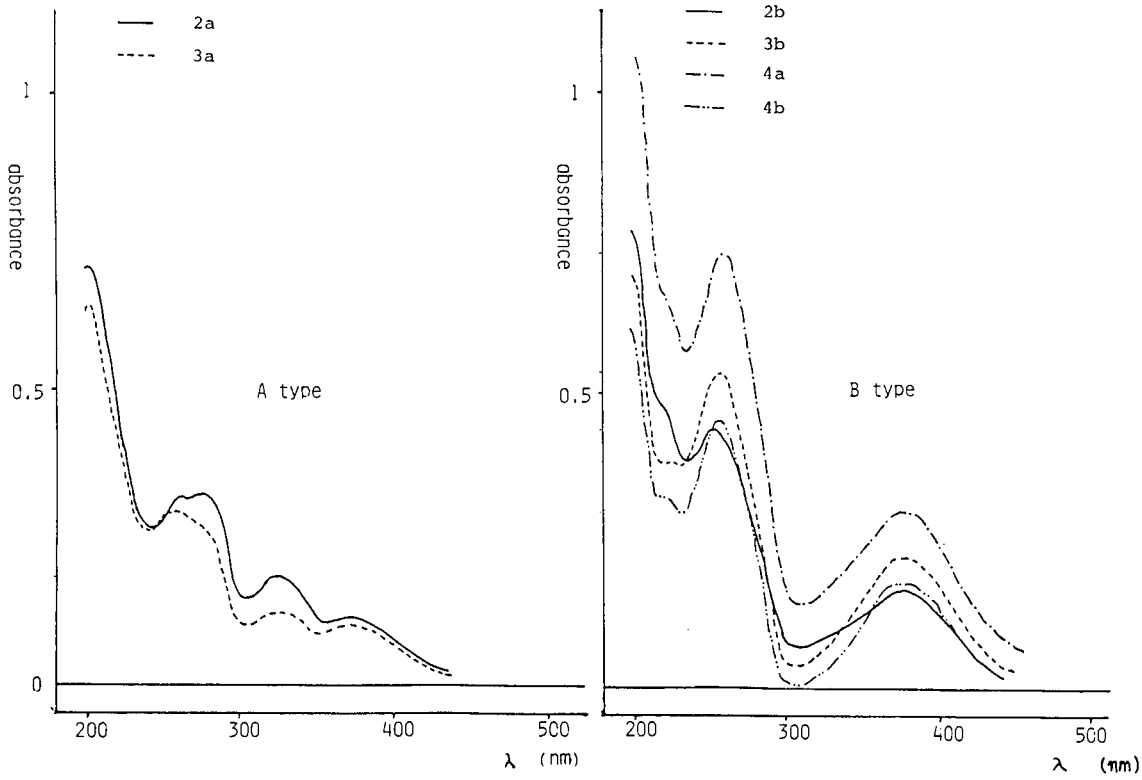


Figure 1

It appeared that the phenomena (of type-B) resulted from steric inhibition of resonance on the basis of free rotation of substituted group on N-1 and methyl amino group on C-6 in pyrimidine ring is restricted by steric repulsion between those groups. The ^{1}H-nmr spectrum of pyrido[2,3-*d*]-pyrimidines **3a, 3b** and **3c** showed a characteristic signal of H on C-6 at δ 6.70, 6.72 and 6.75, and that of pyrrolo-[2,3-*d*]pyrimidines **4a, 4b** and **4c** exhibited a typical signal due to methylenic proton at δ 7.13, 7.17 and 7.17. The downfield shift of **4** is apparently caused by an anisotropic effect of carbonyl group at C-6 due to close proximity of the proton on the methylenic moiety.

The fact that both the major and minor products are derived from the same intermediate **2a** disproved the involvement of **5** in the formation of the major product which, consequently, is not pyridopyrimidine **6**. The only possible structure for the major product is 1,3,7-trimethyl-5-methoxycarbonylmethylenepyrrolo[2,3-*d*]pyrimidine-2,4,5(1*H*,3*H*,5*H*,7*H*)-trione (**4a**).

The most plausible mechanism for the formation of **4a** from **2a** is condensation of the α-carboxylate with the 6-alkylamine group as shown in Chart 1.

EXPERIMENTAL

All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are uncorrected. Mass spectra (MS) were recorded on a JEOL-D-100 instrument. The uv spectra were measured with a Hitachi 340 spectrometer. The ^{1}H-nmr spectra were recorded on a Varian EM-390-NMR spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ values. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Elemental analyses were performed by the staff in Microanalytical Laboratory of this school. Preparative thin-layer chromatography (tlc) was done with Merck precoated silica gel 60 F_{254} plates, 20 x 20 cm, with thickness of 0.25 mm.

Reaction of 1,3-Dimethyl-6-methylaminouracil with DMAD.

A solution of 1,3-dimethyl-6-methylaminouracil (1.69 g, 10 mmoles) with DMAD (1.70 g, 12 mmoles) in methanol (130 ml) was stirred at room temperature for 24 hours. The reaction mixture was concentrated and the precipitate (2.60 g) was collected by suction and purified by preparative tlc with ethanol-benzene (1:9) as an eluent to give dimethyl 2-(1,3-dimethyl-6-methylamino-2,4-dioxopyrimidin-5-yl)fumarate (**2a**), mp 159° (washed with methanol), yield, 1.15 g (37%); ms: m/z 311 (M^+); ^{1}H-nmr (deuteriochloroform): 2.70 (3H, d, J = 6 Hz, NHC*H*$_3$), 3.25, 3.43 (each 3H, s, NCH_3 x 2), 3.67, 3.78 (each 3H, s, ester CH_3 x 2), 4.63 (1H, d, J = 6 Hz, N*H*CH$_3$), 6.90 (1H, s, C=CH-); uv (ethanol): λ max nm (log ϵ) 260 (4.08), 276 (4.09), 326 (3.87), 379 (3.63).

Anal. Calcd. for $C_{13}H_{17}N_3O_6$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.62; H, 5.23; N, 13.98.

Another product was 1,3,8-trimethyl-5-methoxycarbonylpyrido[2,3-*d*]-

pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**3a**) as yellow needles, yield, 210 mg (7.5%), mp 215° (from methanol, lit mp 215-216° [2]); ms: m/z 279 (M^+); ^{1}H-nmr (deuteriochloroform): 3.33, 3.50 and 3.76 (each 3H, s, $=NCH_3$ x 3), 3.88 (3H, s, ester CH_3), 6.70 (1H, s, =CH-); uv (ethanol): λ max nm (log ε) 257 (4.06), 276 (4.04), 326 (3.87), 374 (3.78).

Thermal Reaction of Dimethyl 2-(1,3-dimethyl-6-methylamino-2,4-dioxopyrimidin-5-yl)fumarate (**2a**).

Compound **2a** (250 mg, 0.8 mmole) was heated for 20 minutes with stirring at a bath temperature of 165-175°. The resulting residue gave a mixture of **4a** and **3a** in a ratio of 77:23 on the basis of δ 7.13 (**4a**) and 6.70 (**3a**) by integration of the ^{1}H-nmr (deuteriochloroform) in quantitative yield, and the mixture was treated by preparative tlc with ethanol-benzene (1:9) as an eluent to purify **4a**, 70 mg, together with **3a** (trace), 1,3,7-trimethyl-5-methoxycarbonylmethylenepyrrolo[2,3-*d*]pyrimidine-2,4,6(1*H*,3*H*,5*H*,7*H*)-trione (**4a**), yellow needles, 70 mg, mp 215-216°; ms: m/z 279 (M^+); ^{1}H-nmr (deuteriochloroform): 3.33, 3.47 and 3.72 each 3H, s, NCH_3 x 3), 3.82 (3H, s, ester CH_3), 7.13 (1H, s, =CH-); uv (ethanol): λ max nm (log ε) 257 (4.17), 373 (3.78).

Anal. Calcd. for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.91; H, 4.56; N, 14.92.

Thermal Reaction of **2a** in Methanol.

A solution of **2a** (250 mg, 0.8 mmole) in methanol (5 ml) was heated under reflux for 30 minutes, and after removal of the solvent, the resulting residue gave a mixture of **4a** and **3a** in a ratio of 23:77 on the basis of δ 7.13 (**4a**) and 6.70 (**3a**) by integration of the ^{1}H-nmr (deuteriochloroform) in the quantitative yield. The mixture was treated by preparative tlc with ethanol-benzene (1:9) as an eluent to purify **3a**, 120 mg, together with **4a** (trace).

Reaction of 1,3-Diethyl-6-methylaminouracil with DMAD.

A solution of 1,3-diethyl-6-methylaminouracil (1.97 g, 10 mmoles) and DMAD (1.70 g, 12 mmoles) in methanol (30 ml) was stirred at room temperature for 24 hours. The precipitate (1.50 g) was collected by suction and purified by preparative tlc (ethyl acetate:chloroform = 1:9), extraction with ethylacetate to give dimethyl 2-(1,3-diethyl-6-methylamino-2,4-dioxopyrimidin-5-yl)fumarate (**2b**), 1.28 g (39%), mp 146-147° (washed with methanol); ms: m/z 339 (M^+); ^{1}H-nmr (deuteriochloroform): 1.18 and 1.33 (each 3H, t, $-CH_2CH_3$), 2.72 (3H, d, J = 6 Hz, $NHCH_3$), 3.66 and 3.82 (each 3H, s, ester CH_3 x 2), 3.82 and 3.88 (each 2H, q, $-CH_2CH_3$ x 2), 4.40 (1H, d, J ^{5} 6 Hz, $NHCH_3$), 6.83 (1H, s, =CH-); uv (ethanol): λ max nm (log ε) 255 (4.06), 373 (3.63).

Anal. Calcd. for $C_{15}H_{21}N_3O_6$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.22; H, 6.11; N, 12.51.

Another product was 1,3-diethyl-5-methoxycarbonyl-8-methylpyrido-[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**3b**), 162 mg (5.3%), mp 169° (from methanol); ms: m/z 307 (M^+); ^{1}H-nmr (deuteriochloroform): 1.20 and 1.40 (each 3H, t, $-CH_2CH_3$), 3.52 (3H, s, NCH_3), 3.88 (3H, s, ester CH_3), 4.01 and 4.28 (each 2H, q, $-CH_2CH_3$), 6.72 (1H, s, =CH-); uv (ethanol): λ max nm (log ε) 255 (4.19), 374 (3.82).

Thermal Reaction of Dimethyl 2-(1,3-diethyl-6-methylamino-2,4-dioxopyrimidin-5-yl)fumarate (**2b**).

Compound **2b** (200 mg, 0.58 mmole) was heated for 20 minutes with stirring at a bath temperature of 165-170°. The resulting residue gave a mixture of **4b** and **3b** in a ratio of 86:14 on the basis of δ 7.17 (**4b**) and 6.75 (**3b**) by integration on the ^{1}H-nmr (deuteriochloroform) in quantitative yield, and the mixture was treated by preparative tlc with ethyl acetate:chloroform (1:9) as an eluent to purify **4b**, 123 mg, together with **3b** (trace), 1,3-diethyl-7-methyl-5-methoxycarbonylmethylenepyrrolo-[2,3-*d*]pyrimidine-2,3,6(1*H*,3*H*,5*H*,7*H*)-trione (**4b**), yellow needles, 123 mg, mp 159-160°; ms: m/z 307 (M^+); ^{1}H-nmr (deuteriochloroform): 1.23 and 1.40 (each 3H, t, $-CH_2CH_3$), 3.47 (3H, s, NCH_3), 3.82 (3H, s, ester CH_3), 4.03 and 4.27 (each 2H, q, $-CH_2CH_3$), 7.17 (1H, s, =CH-); uv (ethanol): λ max (log ε) 257 (4.16), 375 (3.75).

Anal. Calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.68. Found: C, 54.81; H, 5.62; N, 13.52.

Thermal Reaction of **2b** in Methanol.

A solution of **2b** (200 mg, 0.59 mmole) in methanol (5 ml) was heated under reflux for 30 minutes, and after removal of the solvent, the resulting residue gave a mixture of **3b** and **4b** in a ratio of 80:20 on the basis of δ 6.75 (**3b**) and 7.17 (**4b**) by integration on the ^{1}H-nmr (deuteriochloroform) in quantitative yield. The mixture was treated by preparative tlc (ethyl acetate:chloroform = 1:9), extraction with ethyl acetate to purify **3b**, 95 mg, together with **4b** (trace).

Reaction of 1,3-Dimethyl-6-ethylaminouracil with DMAD.

A solution of 1,3-dimethyl-6-ethylaminouracil (1.83 g, 10 mmoles) and DMAD (1.70 g, 12 mmoles) in methanol (30 ml) was stirred at room temperature for 20 hours. The reaction mixture was evaporated *in vacuo*. The residue was filtered and washed with chloroform to give a yellow solid (2.25 g, 70%). The crude products were purified by preparative tlc (ethyl acetate:chloroform = 1:9), extraction with ethyl acetate to give dimethyl 2-(1,3-dimethyl-6-ethylamino-2,4-dioxopyrimidin-5-yl)fumarate (**2c**), 936 mg (29%), mp 164-165° (washed with methanol); ms: m/z 325 (M^+); ^{1}H-nmr (deuteriochloroform): 1.19 (3H, t, $-CH_2CH_3$), 2.80-3.18 (2H, br, $-NHCH_2CH_3$), 3.28 and 3.65 (each 3H, s, N-CH_3), 3.72 and 3.82 (each 3H, s, ester CH_3), 4.15-4.32 (1H, br, $-NHCH_2CH_3$), 6.96 (1H, s, =CH-); uv (ethanol): λ max nm (log ε) 254 (3.92), 374 (3.57).

Anal. Calcd. for $C_{16}H_{19}N_3O_6$: C, 51.68; H, 5.89; N, 12.92. Found: C, 51.62; H, 5.82; N, 12.68.

Another product was 1,3-dimethyl-5-methoxycarbonyl-8-ethylpyrido-[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**3c**), 48 mg, mp 162-163° (from methanol); ms: m/z 293 (M^+); ^{1}H-nmr (deuteriochloroform): 1.30 (3H, t, $-CH_2CH_3$), 3.33 and 3.72 (each 3H, s, NCH_3), 3.88 (3H, s, ester CH_3), 4.05 (2H, q, $-CH_2CH_3$), 6.75 (1H, s, =CH-); uv (ethanol): λ max nm (log ε 252 (3.58), 374 (3.13).

Anal. Calcd. for $C_{13}H_{15}N_3O_5$: C, 53.24; H, 5.15; N, 14.32. Found: C, 53.17; H, 5.20; N, 14.26.

Thermal Reaction of Dimethyl 2-(1,3-dimethyl-6-ethylamino-2,4-dioxopyrimidin-5-yl)fumarate (**2c**).

Compound **2c** (233 mg, 0.71 mmole) was heated for 20 minutes with stirring at a bath temperature of 150-152°. The yield was quantitative, and the ratio of two products was 89.5:10.5. The mixture was recrystallized from methanol to give 1,3-dimethyl-7-ethyl-5-methoxycarbonylmethylenepyrrolo[2,3-*d*]pyrimidine-2,4,6(1*H*,3*H*,5*H*,7*H*)-trione (**4c**), yellow crystals, 168 mg (80%), mp 171-172° (from methanol); ms: m/z 293 (M^+); ^{1}H-nmr (deuteriochloroform): 1.33 (3H, t, $-CH_2CH_3$), 3.37 and 3.74 (each 3H, s, NCH_3), 3.85 (3H, s, ester CH_3), 4.02 (2H, q, $-CH_2CH_3$), 7.17 (1H, s, =CH-); uv (ethanol): λ max nm (log ε) 256 (4.02), 380 (3.60).

Anal. Calcd. for $C_{13}H_{15}N_3O_5$: C, 53.24; H, 5.15; N, 14.32. Found: C, 53.17; H, 5.09; N, 14.27.

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