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Unusual reactions of 6-amino-1,3-dimethyluracil with some aliphatic aldehydes

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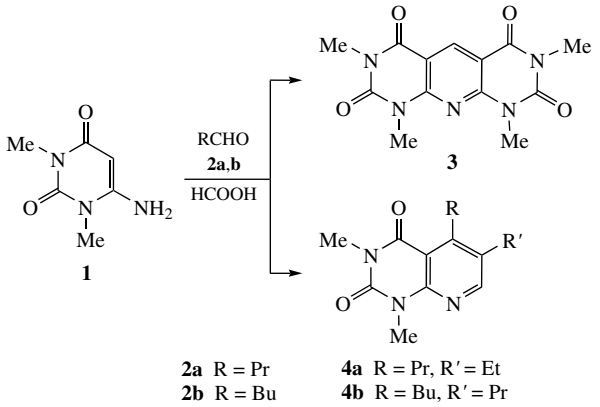
6-Amino-1,3-dimethyluracil reacts with two molecules of alkanals (butanal or pentanal) in formic acid to give 1,3,7,9-tetramethyl-2,4,6,8-tetraoxopyrido[2,3-*d*][6,5-*d'*]dipyrimidine and the corresponding 3,4-dialkyl-substituted 6,8-dimethyl-5,7-dioxopyrido[2,3-*d*]-pyrimidines.

Compounds with a broad spectrum of biological activity have been found among derivatives of pyrido[2,3-*d*]pyrimidines.[1–3] A number of 2,4-dioxopyrimido[2,3-*d*]pyrimidine derivatives were synthesized from 6-amino-5-formyl-1,3-dimethyluracil, which was obtained by formylation of 6-amino-1,3-dimethyluracil with acetic formic anhydride[4] or Vilsmeier reagent.[5,6] 6-Amino-1,3-dimethyluracil reacts with aldehydes in water to give hetero-aryl-substituted bis(6-amino-1,3-dimethyluracil-5-yl)methanes.[7] Reaction between 6-amino-5-formyluracils and 1,3-dicarbonyl compounds affords 6,7-substituted pyrido[2,3-*d*]pyrimidines.[8]

Here, we report that heating of 6-amino-1,3-dimethyluracil **1** with alkanals **2a**,**b** in formic acid results in 1,3,7,9-tetramethyl-2,4,6,8-tetraoxopyrido[2,3-*d*][6,5-*d'*]dipyrimidine **3** and 3,4-di-alkyl-substituted 6,8-dimethyl-5,7-dioxopyrido[2,3-*d*]pyrimidines **4a**,**b** (Scheme 1).†



Scheme 1

The signals of methyl groups in the ^{1}H NMR spectrum of compound **3** are observed as two hexaproton singlets at δ 3.51 and 3.76 ppm. The proton of the pyridine ring of product **3** manifests itself as a singlet signal at δ 9.18 ppm. The mass spectrometry data of compound **3** matches the proposed structure. Judging from the melting point, pyridodipyrimidine **3** that we obtained is identical to the coupling product of 6-amino-1,3-dimethyluracil with 6-amino-5-formyl-1,3-dimethyluracil.[8]

The structure of pyridopyrimidines **4a**,**b** was determined by mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy of these compounds, including the 2D ^{1}H-^{13}C HSQC, HMBC experiments for product **4a**. The carbonyl carbons C^2 and C^4 were identified by the cross-peaks with *N*-methyl protons in the HMBC spectrum (Figure 1), the C^2 carbon (δ_C 152.75 ppm) having cross-peaks with protons of both methyl groups, whereas C^4 (δ_C 161.78 ppm) has a cross-peak with one group only. The H$^{1'}$ methylene protons of the propyl residue give cross-peaks with the C^{4a}, C^5 and C^6 carbons, whereas the H$^{1''}$ protons of the ethyl residue are bound by long-range coupling with the C^5, C^6 and C^7 carbons.

† *Reaction of 6-amino-1,3-dimethyluracil* **1** *with alkanals* **2a**,**b**. 6-Amino-1,3-dimethyluracil **1** (0.5 g, 3.2 mmol) was stirred for 5 h at 50 °C with 12.8 mmol of the corresponding alkanal in formic acid (5 ml). The reaction mixture was then concentrated by 3/4 *in vacuo*, and the residue was treated with ethanol (3 ml). The precipitate of compound **3** was filtered and washed with ethanol (2 ml). The yield of **3** was 25–30%, mp 320–322 °C (lit.,[8] mp 321–323 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.51 (s, 6H, Me), 3.76 (s, 6H, Me), 9.18 (s, 1H, H^5). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.53 (MeN^3, MeN^7), 30.02 (MeN^1, MeN^9), 106.41 (C^{4a}, C^{5a}), 140.88 (C^5), 151.15 (C^{9a}, C^{10a}), 153.59 (C^2, C^8), 159.86 (C^4, C^6). MS, *m*/*z* (%): 303 [M$^+$] (100), 275 (23), 218 (12), 191 (77). Found (%): C, 51.55; H, 4.12; N, 22.81. Calc. for $C_{13}H_{13}N_5O_4$ (%): C, 51.48; H, 4.32; N, 23.09.

The mother liquor from the reaction mixture was combined with the washing alcohol and diluted with water (1:1). The products **4** that precipitated were filtered and recrystallized from high-boiling light petroleum.

*6-Ethyl-1,3-dimethyl-5-propyl-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione* **4a**: yield 55–60%, mp 109–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.11 (t, 3H, H$^{3'}$, *J* 7.3 Hz), 1.26 (t, 3H, H$^{2''}$, *J* 7.6 Hz), 1.57 (m, 2H, H$^{2'}$), 2.72 (q, 2H, H$^{1''}$, *J* 7.6 Hz), 3.25 (m, 2H, H$^{1'}$), 3.46 (s, 3H, MeN^3), 3.69 (s, 3H, MeN^1), 8.38 (s, 1H, H^7). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 14.77 (C$^{3'}$), 15.65 (C$^{2''}$), 22.92 (C$^{1''}$), 23.96 (C$^{2'}$), 28.51 (MeN^3), 29.89 (MeN^1), 31.37 (C$^{1'}$), 108.34 (C^{4a}), 133.59 (C^6), 150.58 (C^{8a}), 151.21 (C^2), 152.75 (C^7), 155.13 (C^5), 161.78 (C^4). MS, *m*/*z* (%): 261 [M$^+$] (65), 246 (100), 244 (65), 233 (19), 218 (23). Found (%): C, 64.15; H, 7.15; N, 15.98. Calc. for $C_{14}H_{19}N_3O_2$ (%): C, 64.35; H, 7.33; N, 16,08.

*5-Butyl-1,3-dimethyl-6-propyl-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione* **4b**, yield 55–60%, mp 85–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.99 (t, 3H, Me, *J* 6.9 Hz), 1.01 (t, 3H, Me, *J* 7.4 Hz), 1.43–1.56 (m, 4H, CH_2), 1.62 (m, 2H, CH_2), 2.65 (m, 2H, H$^{1''}$), 3.27 (m, 2H, H$^{1'}$), 3.47 (s, 3H, MeN^3), 3.69 (s, 3H, MeN^1), 8.35 (s, 1H, H^7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.86 (Me), 13.98 (Me), 23.43 (CH_2), 24.44 (CH_2), 28.52 (MeN^3), 29.29 (CH_2), 29.89 (MeN^1), 31.76 (CH_2), 108.42 (C^{4a}), 132.01 (C^6), 150.61 (C^{8a}), 151.22 (C^2), 153.23 (C^7), 155.57 (C^5), 161.75 (C^4). MS, *m*/*z* (%): 289 [M$^+$] (46), 274 (21), 272 (19), 261 (24), 260 (100), 247 (50), 246 (23), 232 (14), 219 (16), 218 (38). Found (%): C, 66.25; H, 8.15; N, 14.38. Calc. for $C_{14}H_{19}N_3O_2$ (%): C, 66.41; H, 8.01; N, 14.52.

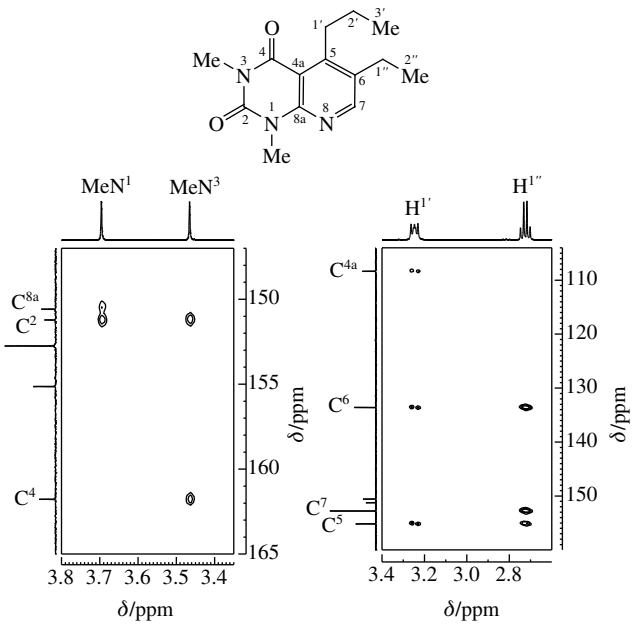
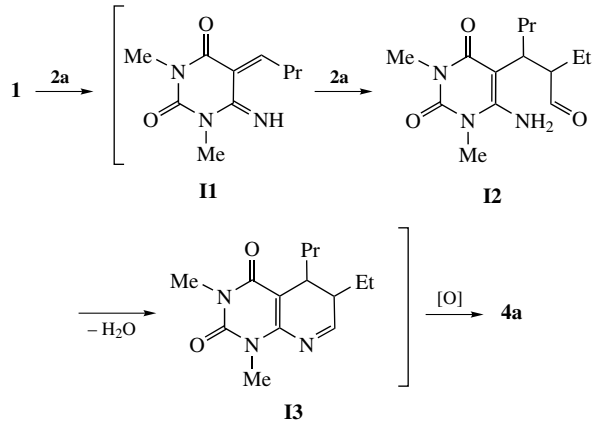


Figure 1 Fragments of the 2D ^{1}H-^{13}C HMBC spectrum (500 MHz, $CDCl_3$) of compound **4a**.

Products **4** are apparently formed *via* a series of intermediates **I1**–**I3** (Scheme 2 shows the reaction of compound **1** with butanal as an example).



Scheme 2

Knoevenagel product **I1** acts as a Michael acceptor for the second butanal molecule to give intermediate **I2**, which is converted to the cyclic intermediate **I3**. Aromatization (oxidation) of **I3** results in pyridopyrimidine **4**. Intermediate **I3** can be oxidized by atmospheric oxygen or by components of the reaction mixture. Apparently, redox processes thus occurring provide oxidation **I3** → **4** and also produce formaldehyde, which is required for the formation of product **3**. Note that the heating of 6-amino-1,3-dimethyluracil **1** in formic acid in the absence of alkanals **2a**,**b** did not give product **3**. However, the heating of **1** in formic acid in the presence of formaldehyde produced pyridodipyrimidine **3**.‡

In conclusion, a new reaction type has been discovered where 6-aminouracil actually reacts with two molecules of an alkanal, which are linked together and, in effect, react as a 1,3-dicarbonyl reagent. These transformations make possible to access 5,6-disubstituted pyrido[2,3-*d*]pyrimidines in one stage from available reactants.

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‡ *Reaction of 6-amino-1,3-dimethyluracil* **1** *with formaldehyde*. 6-Amino-1,3-dimethyluracil **1** (0.05 g, 0.3 mmol) was stirred with 37% formaldehyde solution (0.1 ml, 1.2 mmol) in formic acid (3 ml) at 50 °C for 5 h. The mixture was then evaporated to dryness *in vacuo* and the residue was treated with ethanol (3 ml). The precipitate of compound **3** was filtered, washed with ethanol (2 ml) and recrystallized from DMF. The yield of compound **3** was 0.032 g (67%). Judging by the ^{1}H NMR and mass spectra, the resulting product was identical to compound **3** obtained as described above.