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Some Novel Reactions of 1,3-Dimethyluracils. II.[1,2] Studies on New Stable Pyrimidine Ring-Opened Compounds

Norio Kawahara,*,[a] Tsuneo Itoh,[b] Haruo Ogura,[b] and Kyoichi A Watanabe[c]

Hokkaido College of Pharmacy,[a] Katsuraoka-cho, Otaru-shi, 047-02, Japan, School of Pharmaceutical Sciences, Kitasato University,[b] Shirokane, Minato-ku, Tokyo, 108, Japan and Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division of Graduate School of Medicinal Sciences, Cornell University,[c] Rye, New York, 10580, U.S.A.

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N,N'-Dialkyl-*N*-[3-methoxy-3-dialkylamino-2-(3-methoxycarbonylpropioloyl) acryloyl]ureas (**3**) were synthesized by coupling of 1,3-dialkyl-6-(*N*-substituted)aminouracils (**2**) and dimethyl acetylenedicarboxylate (DMAD). Compounds (**3**) are stable crystalline materials at room temperature, but on heating in DMF, they undergo cyclization, giving rise to the pyrido[2,3-*d*]pyrimidine derivatives. These compounds were characterized by ^{1}H-nuclear magnetic resonance (NMR), ^{13}C-NMR, mass spectral and elemental analyses.

Keywords——pyrimidine ring-opened compound; DMAD; ^{1}H-NMR; thermal cyclization; ^{13}C-NMR; addition reaction

Reactions of 6-aminouracils with dimethyl acetylenedicarboxylate (DMAD) are widely used for the preparation of various pyrido[2,3-*d*]pyrimidines.[3] In connection with our continuing studies on heterocyclic compounds, we became interested in the addition reactions of nucleic acid bases with DMAD and recently reported some results.[4] It was known that the reaction of 1-alkyl-6-aminouracil derivatives with DMAD gave the 5-(3-methoxycarbonyl-2-propioloyl)uracils under aprotic conditions, and the pyridopyrimidines in protic solvents.[3]

Recently, Andersen and Broom[5] reported that the treatment of 1,3-dimethyl-6-aminouracil with DMAD in DMSO gave the pyrimidine ring-opened intermediate, which was converted to the propynoyl derivative simply by gentle warming or by allowing the solution to stand at room temperature. In this report, we present full experimental details of the synthesis of new stable pyrimidine ring-opened compounds.

1,3-Dimethyl-6-pyrrolidinouracil (**2a**) was synthesized by warming of 6-chloro-1,3-dimethyluracil (**1**) with pyrrolidine in EtOH. 1,3-Dimethyl-6-dimethylaminouracil (**2b**) and 6-dimethyamino-1,3-diethyluracil (**2c**) were prepared by stirring of 6-chloro-1,3-dimethyluracil (**1**) and 6-chloro-1,3-diethyluracil (**1**, R=Et), respectively, with dimethylamine at room temperature.

1,3-Dimethyl-6-pyrrolidinouracil (**2a**) was treated with DMAD at room temperature in CH_2Cl_2 and the reaction was followed by thin layer chromatography (TLC) (MeOH/EtOAc=1/1). A white precipitate appeared and gradually increased in quantity. The reaction mixture was stirred for 6 h, then dry ether was added and the precipitate was filtered off in 81% yield.

The ^{1}H-NMR spectrum of the recrystalized product [**3a**, mp=239°C (dec.)] showed a δ 2.98 doublet (J=4 Hz) which was rapidly converted to a singlet upon addition of D_2O, with concomitant disappearance of a broad signal at δ 8.10. These data are very similar to those of the ring-opened intermediate reported by Anderson and Broom.[5]

The structure of this compound (**3a**) was assigned as *N,N*^{1}-dimethyl-*N*-[3-methoxy-3-pyrrolidino-2-(3-methoxycarbonylpropioloyl)-acryloyl]urea based on the MS, ^{1}H-nuclear magnetic resonance (NMR), ^{13}C-NMR and elemental analyses. Upon continued heating in DMF solution, this compound (**3a**) was converted to 1,3-dimethyl-5-(3-methoxycarbonyl-propioloyl)-6-pyrrolidinouracil (**4**, mp=257—261°C). It is interesting to note that compound

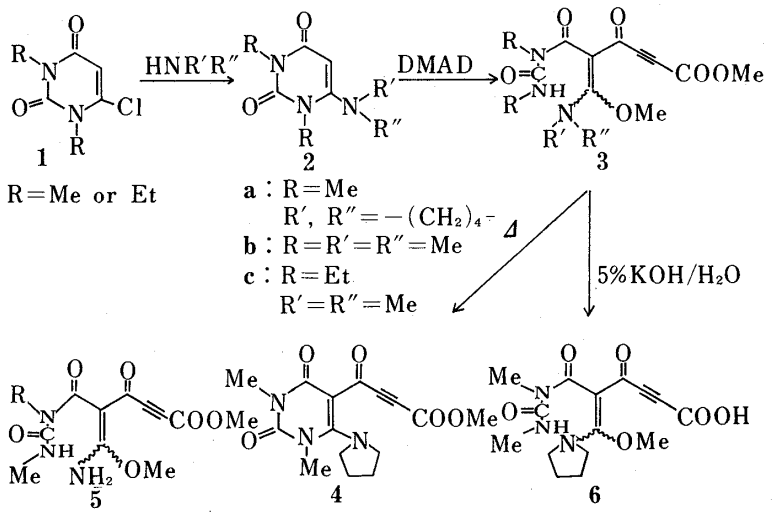

Fig. 1

(**5**), structurally similar to **3a**, is an unstable intermediate which readily cyclizes at room temperature to give a **5**-substituted pyrimidine analogous to **4**. Compound (**3a**), however, was found to be stable at room temperature and it required heating (refluxing in DMF) to effect the cyclization to **4**, which was obtained only in low yield (20%). The ring-opened compound (**3a**) was also prepared in other aprotic solvents (DMSO, THF) under the same reaction conditions.

The above compound (**3a**) was treated in 5% KOH/H_2O at room temperature for 2 h, then acidified. A crystalline compound [**6**, mp=224—228°C (dec.)] was obtained as the only isolable product from the mixture by ion exchange chromatography (Amberlite XAD-2).

In order to confirm the structure of the product (**3a**), the addition reactions of 1,3-dimethyl-6-dimethylaminouracil (**2b**) and 1,3-diethyl-6-dimethylaminouracil (**2c**) with DMAD under similar conditions were studied. The ring-opened products [**3b**, mp=240°C (dec.), and **3c**, mp=220°C (dec.)] were also obtained in 40% and 43% yields, respectively, but we could not obtain a stable ring-opened compound by treatment of 6-(*N*-nonsubstituted)aminouracil with DMAD under the conditions described above.

Thus, it may be concluded that 1,3-dialkyl-6-(*N*-substituted)aminouracils (**2**) give stable pyrimidine ring-opened products upon treatment with DMAD in aprotic solvents at room temperature, whereas 1,3-dialkyl-6-aminouracils (**2**, R′=R″=H) do not.

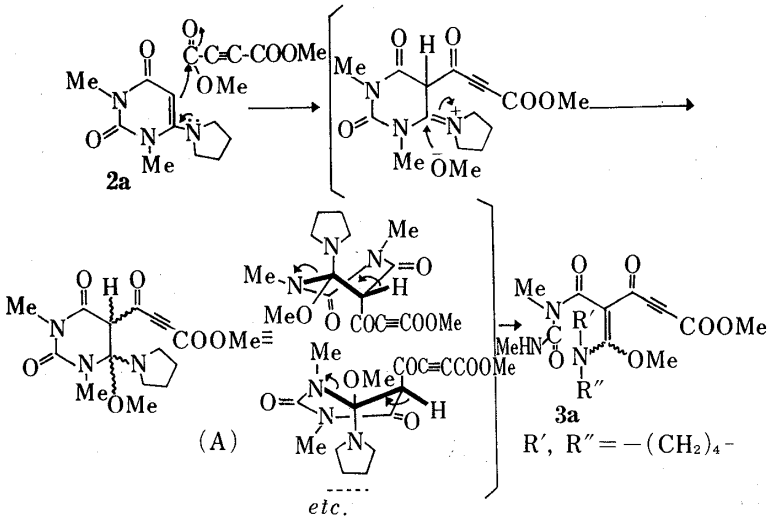

Fig. 2

On the basis of molecular model examination, the formation of **3** can be formulated as shown in Fig. 2. It may be assumed that after the nucleophilic addition of **2** to DMAD, when the C_5–H bond keeps an anti-coplanar relationship with the N_1–C_6 bond in intermediate (A), the pyrimidine ring breaks to give **3**.

Although the steric relationship between the methoxycarbonylpropioloyl group and the pyrrolidino group in the intermediate (A) is not clear, the ring-opened product (**3**) is expected to be *E*-form if A has a *trans* configuration, and *Z*-form if A is *cis*.

The ^{1}H and ^{13}C-NMR spectra of **3b** and **3c** showed that R′ and R″ are non-equivalent (^{1}H-NMR: **3b**, R′=3.14, R″=3.27; **3c**, R′=2.97, R″=3.10). The results can be interpreted by visualizing the actual structure of **3** as a resonance hybrid containing a double bond [R′(R″)N_1^+=C_6(OMe)–], and the non-equivalence of R′ and R″ is then due to this rotational barrier.

The reason why **3a** resists cyclization compared to the 6-amino compound (**5**) is not obvious, but it may be chiefly attributed to the steric hindrance caused by the close proximity of the –NR′(R″), –NHR and C_2-carbonyl groups.

Experimental

Melting points were determined on a micro hot-stage apparatus (Mitamura) and are uncorrected. IR spectra were taken on a Hitachi 215 infrared spectrophotometer. NMR spectra (^{1}H and ^{13}C) were recorded on a JEOL JNM-FX100 spectrometer with tetramethylsilane (TMS) as an internal standard; s=singlet, d=doublet, t=triplet and m=multiplet. Mass spectra (MS) were obtained on a GCMS-9000 spectrometer (Shimadzu-LKB) by the direct insertion method. The ultraviolet spectra were taken with a Hitachi 200-20 spectrophotometer.

1,3-Dimethyl-6-pyrrolidinouracil (2a)[2]——Pyrrolidine (2.0 ml) was added to a suspension of 6-chloro-1,3-dimethyluracil (**1**, R=CH_3, 2.0 g) in EtOH (15 ml). The mixture was stirred overnight at room temperature, then the solvent was evaporated off under reduced pressure.

The residual solid was extracted with three portions of EtOAc and the extracts were concentrated to give crystalline material (2.4 g). The crude product was purified by recrystallization from EtOAc to give 1,3-dimethyl-6-pyrrolidinouracil (**2a**) mp=83—85°C. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.17 (4H, m, –CH_2CH_2–), 3.13—3.26 (4H, m, –CH_2NCH_2–), 3.32 (3H, s, N–CH_3), 3.42 (3H, s, N–CH_3), 5.13 (1H, s, vinylic). MS *m/e*: 209 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 1635 (C=O). UV λ_{max}^{MeOH} (log ε): 203 (4.05), 215 (4.03), 243 (3.46), 279 (4.30). ^{13}C-NMR ($CDCl_3$) δ: 25.39 (–CH_2CH_2–), 27.63 (N–Me), 35.04 (N–Me), 50.92 (–CH_2NCH_2–), 82.26 (–C̲H=C–), 153.26 (–CH=C̲N–), 157.20 (C=O), 162.96 (C=O).

1,3-Dimethyl-6-dimethylaminouracil (2b)——An MeOH (10 ml) solution of 6-chloro-1,3-dimethyluracil (**1**, R=CH_3, 400 mg) was treated with 30% aq. $HNMe_2$ (1 ml). After being stirred for 2 h at room temperature, the reaction mixture was concentrated *in vacuo*.

The residue was extracted with ether and the organic layer was washed with H_2O and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue (503 mg) was purified by silica gel chromatography using benzene–EtOAc (8: 2) as an eluent to give 1,3-dimethyl-6-dimethylaminouracil (**2b**, 417 mg). Recrystallization from ether gave **2b** as fine plates, mp=86—86.5°C. *Anal.* Calcd for $C_8H_{13}N_3O_2$ (183.21): C, 52.44; H, 7.15; N, 22.94. Found: C, 52.57; H, 7.13; N, 22.97. MS *m/e*: 183 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.74 (6H, s, CH_3NCH_3), 3.32 (3H, s, N–CH_3), 3.40 (3H, s, N–CH_3), 5.20 (1H, s, vinylic).

1,3-Diethyl-6-dimethylaminouracil (2c)——An MeOH (10 ml) solution of 6-chloro-1,3-diethyluracil (**1**, R=CH_2CH_3, 1.0 g) was treated with 30% aq. $HNMe_2$ (2 ml). The mixture was stirred overnight at room temperature, and the solvent was evaporated off *in vacuo*. The residue was extracted with ether and the ethereal layer was washed with H_2O and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue (0.88 g) was purified by silica gel column chromatography using benzene–EtOAc (9: 1) as an eluent to give a pale yellow oil (**2c**) whose homogeneity was confirmed by TLC (benzene: EtOAc=1: 3). MS *m/e*: 211 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz, N–CH_2C̲H_3), 1.27 (3H, t, J=7 Hz, N–CH_2C̲H_3), 2.73 (6H, s, CH_3NCH_3), 3.96 (2H, q, J=7 Hz, N–C̲H_2CH_3), 3.99 (2H, q, J=7 Hz, N–C̲H_2CH_3), 5.22 (1H, s, vinylic).

***N,N′*-Dimethyl-*N*-[3-methoxy-3-pyrrolidino-2-(3-methoxycarbonylpropioloyl)acryloyl]urea (3a)**——DMAD (1.1 ml) was added to a dry CH_2Cl_2 (15 ml) solution of 1,3-dimethyl-6-pyrrolidinouracil (**2a**, 1.1 g) at room temperature. The mixture was stirred at room temperature for 6 h. A precipitate developed in the reaction flask. Dry ether was added, then the pale yellow crystals were filtered off and washed with ether to give 1.49 g of **3a**. The crude product was recrystallized from EtOH, mp=239°C (dec.). *Anal.* Calcd for $C_{16}H_{21}N_3O_6$ (351.35): C, 54.69; H, 6.02; N, 11.96. Found: C, 54.55; H, 6.06; N, 11.82. MS *m/e*: 351 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3440 (NH), 3175 (NH), 1735 (CO_2Me), 1715 (CO), 1630 (CO), 1580 (NH). ^{1}H-NMR ($CDCl_3$) δ: 1.75—2.28 (4H, m, CH_2CH_2), 2.98 (3H, d, J=4 Hz, $NHCH_3$), 3.36—3.60 (4H, m, CH_2NCH_2), 3.36 (3H, s,

NCH_3), 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 8.10 (1H, broad, NH). ^{13}C-NMR (pyridine-d_5) δ: 23.98 (–$\underline{C}H_2CH_2$–), 24.17 (–$CH_2\underline{C}H_2$–), 26.56 (NCH_3), 30.16 (NCH_3), 47.37 ($\underline{C}H_2NCH_2$), 50.63 (–$CH_2N\underline{C}H_2$–), 51.56 (OCH_3), 52.97 (OCH_3), 94.58 (–$\underline{C}\equiv$C–), 95.56 (–C$\equiv\underline{C}$–), 145.46 (–$\underline{C}$=C–), 158.37 (–C=$\underline{C}$–), 160.90 (CO), 163.05 (CO), 167.34 (CO), 168.46 (CO). **3a** was also obtained in 80% (DMSO) and 43% (THF) yields.

***N,N'*-Dimethyl-*N*-[3-methoxy-3-dimethylamino-2-(3-methoxycarbonylpropioloyl) acryloyl] urea (3b)**——DMAD (0.2 ml) was added to a dry tetrahydrofuran (9 ml) solution of 1,3-dimethyl-6-dimethylaminouracil (**2c**, 145 mg) at room temperature. The mixture was stirred at room temperature for 48 h. A precipitate developed in thereaction flask. Dry ether was added and the pale yellow solid was filtered off and washed with ether to give 110 mg of **3b**. The crude product was recrystallized from EtOH, mp=240°C (dec.). *Anal.* Calcd for $C_{14}H_{19}N_3O_6$ (325.32): C, 51.68; H, 5.89; N, 12.92. Found: C, 51.69; H, 5.85; N, 13.07. IR ν_{max}^{KBr} cm^{-1}: 3410 (NH), 1735 (CO_2Me), 1705 (CO), 1630 (CO), 1580 (NH). MS *m/e*: 325 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.92 (3H, d, J=4 Hz, $NHCH_3$), 3.14 (3H, s, NCH_3), 3.27 (3H, s, NCH_3), 3.34 (3H, s, NCH_3), 3.76 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 9.26 (1H, broad, NH). On irradiation at δ 9.26, the δ: 2.92 doublet was converted to a singlet. ^{13}C-NMR ($CDCl_3$) δ: 26.80 (NCH_3), 32.06 (NCH_3), 38.59 (NCH_3), 41.94 (NCH_3), 51.36 (OCH_3), 52.58 (OCH_3), 93.56 (–$\underline{C}\equiv$C–), 94.34 (–C$\equiv\underline{C}$–), 146.48 (–$\underline{C}$=C–), 160.56 (–C=$\underline{C}$–), 163.05 (CO), 163.73 (CO), 166.41 (CO), 168.07 (CO).

***N,N'*-Diethyl-*N*-[3-methoxy-3-dimethylamino-2-(3-methoxycarbonylpropioloyl) acryloyl] urea (3c)**——DMAD (1.4 ml) was added to a dry tetrahydrofuran (20 ml) solution of 1,3-diethyl-6-dimethylaminouracil (**2c**, 1.2 g). The mixture was stirred at room temperature for 2 d. To complete the reaction, further addition of DMAD (2.8 ml) and refluxing for 5 h were necessary. Ether was added to the cooled reaction mixture to develop a crystalline solid precipitate.

The crude material (0.8 g) obtained was recrystallized from MeOH to give **3c**, mp=220°C (dec.). *Anal.* Calcd for $C_{16}H_{23}N_3O_6$ (353.37): C, 54.39; H, 6.56; N, 11.89. Found: C, 54.34; H, 6.49; N, 11.90. MS *m/e*: 353 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3425 (NH), 1735 (CO_2Me), 1630 (CO), 1575 (NH). ^{1}H-NMR (DMSO-d_6) δ: 0.8—1.3 (6H, m, 2×$CH_2\underline{C}H_3$), 2.97 (3H, s, NCH_3), 3.10 (3H, s, NHC_3), 3.55 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.50—4.10 (4H, m, 2×$N\underline{C}H_2CH_3$), 8.67 (1H, m, NH). ^{13}C-NMR (DMSO-d_6) δ: 12.82 ($CH_2\underline{C}H_3$), 14.28 ($CH_2\underline{C}H_3$), 33.38 (NCH_3), 37.04 (NCH_3), 40.88 ($N\underline{C}H_2CH_3$), 42.05 ($N\underline{C}H_2CH_3$), 50.29 (OCH_3), 51.85 (OCH_3), 91.22 (–$\underline{C}\equiv$C–), 94.68 (–C$\equiv\underline{C}$–), 145.16 (–$\underline{C}$=C–), 159.84 (–C=$\underline{C}$–), 160.66 (CO), 163.00 (CO), 165.88 (CO), 167.19 (CO). UV λ_{max}^{KBr} (log ε: 217 (sh, 4.15), 248 (sh, 3.96), 342 (4.26).

1,3-Dimethyl-5-(3-methoxycarbonylpropioloyl)-6-pyrrolidinouracil (4)——A solution of **3a** (178 mg) in DMF (3 ml) was refluxed for 2 h under a nitrogen stream. After cooling, the reaction mixture was poured into ice-water and extracted with $CHCl_3$. The combined extract was washed with H_2O, then dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (Wakogel C-200, 6 g) using $CHCl_3$ as an eluent to give a ring-closed compound (**4**, 32.2 mg) which was recrystallized from MeOH–ether, mp=257—261°C. *Anal.* Calcd for $C_{15}H_{17}N_3O_5$ (319.31): C, 56.42; H, 5.37; N, 13.16. Found: C, 56.66; H, 5.43; N, 13.23. MS *m/e*: 319 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1745 (CO_2Me), 1725 (CO), 1610 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.4 (4H, m, –CH_2CH_2–), 3.27 (3H, s, NCH_3), 3.37 (3H, s, NCH_3), 3.89 (3H, s, OCH_3), 4.0—4.5 (4H, m, –CH_2NCH_2–). ^{13}C-NMR ($CDCl_3$) δ: 25.63 (–CH_2CH_2–), 27.14 (NCH_3), 30.80 (NCH_3), 52.68 (OCH_3), 54.63 (–CH_2NCH_2–), 88.83 (–$\underline{C}\equiv$C–), 110.23 (–C$\equiv\underline{C}$–), 136.00 (–$\underline{C}$=C–), 158.22 (–C=$\underline{C}$–), 159.39 (CO), 163.24 (CO), 164.24 (CO), 165.82 (CO).

***N,N'*-Dimethyl-*N*-[3-methoxy-3-dimethylamino-2-(3-carboxypropioloyl)acryloyl]urea (6)**——A solution of compound **3a** (351 mg) in 5% KOH/H_2O (10 ml) was allowed to stand at room temperature for 2 h. When the mixture was acidified with dil. HCl, a white solid was deposited. The crude material was filtered off and purified by ion exchange chromatography (Amberlite XAD-2) using MeOH as an eluent to give 185 mg of **6**, mp=224—228°C (dec.). MS *m/e*: 337 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.85 (4H, m, –CH_2CH_2–), 2.75 (3H, d, J=4 Hz, $NHCH_3$), 3.11 (3H, s, NCH_3), 3.55 (3H, s, OCH_3), 3.38 (4H, –CH_2NCH_2–), 8.60 (1H, broad, NH).

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