[Chem. Pharm. Bull. 34(11)4585—4589(1986)]

Reaction of 5-Bromouridine Derivatives with Dimethyl Malonate Carbanion. A Novel Entry to the Synthesis of Uridine-5-acetic Acids[1)]

HIDEO INOUE,* NAOMI SAITO, and TOHRU UEDA

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan

(Received May 12, 1986)

The reaction of N^3,5′-*O*-dibenzoyl-2′,3′-*O*-isopropylidene-5-bromouridine (**1**) with dimethyl malonate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene afforded a 5-malonate ester derivative (**2**) in high yield. Uridine-5-acetic acid (**7**) and its methyl ester (**4**), minor nucleosides in transfer ribonucleic acids, could be readily obtained from **2** *via* removals of one carboxyl function and protecting groups. Treatment of N^3,5′-*O*-dibenzoyl-2′,3′-*O*-isopropylideneuridine (**8**) with the carbanion of ethyl acetoacetate caused degradation of the base moiety to give an N^3-benzoyl-ribosylurea derivative (**9**) in good yield. Possible mechanisms of these reactions are proposed.

Keywords——5-bromouridine; uridine-5-malonate; uridine-5-acetate; dimethyl malonate; DBU; uridine; ribosylurea

In the synthesis of pyrimidine nucleoside analogs, transformations of 5-halogenopyrimidine nucleosides have been widely used.[2)] One of the methods involves reactions with nucleophiles to give 5- and/or 6-substituted derivatives. We have previously demonstrated that the reactions are initiated by the addition of nucleophiles to C-6 of the uracil and cytosine moieties.[3-5)] Thus, a 5-bromouridine derivative reacts with cyanide ion to afford a 6-cyanouridine as a result of cine substitution.[3)] Further, the reaction with 1,3-dithiane anion leads to the formation of a 5-bromo-5,6-dihydro-6-dithianyluridine, which can be further transformed into a 6-formyluridine.[6)] Recently, we have successfully applied such a reaction to an intramolecular cyclization in the synthesis of 2′-deoxy-6,2′-methanouridine.[7)] This paper deals with the reaction of a 5-bromouridine derivative with a carbanion of dimethyl malonate, unexpectedly providing a 5-malonate.

We chose N^3,5′-*O*-dibenzoyl-2′,3′-*O*-isopropylidene-5-bromouridine (**1**) as a reaction substrate. The N^3-benzoyl group was introduced to prevent dissociation of the N^3-proton of the uracil ring in the reaction medium, and furthermore, this electron-withdrawing group was expected to affect the α,β-unsaturated carbonyl system of the base so as to accelerate nucleophilic attack at the C-6 position. Compound **1** was prepared by the reaction of 2′,3′-*O*-isopropylidene-5-bromouridine with benzoyl chloride (BzCl) in dichloromethane in the presence of dimethylaminopyridine (DMAP) and triethylamine at room temperature.[8)] Then, **1** was treated with dimethyl malonate (1.1 eq) in dry tetrahydrofuran (THF) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.4 eq) at room temperature. After 15 h, analysis of the reaction mixture by thin-layer chromatography (TLC) indicated that the reaction had proceeded almost completely[9)] to give a single product. Purification on a column of silica gel gave a foam, which was identified as a uridine-5-malonate derivative (**2**, 95% yield) on the basis of nuclear magnetic resonance (NMR) spectral and mass spectral (MS) analyses.

Treatment of **2** with sodium methoxide in methanol at 50 °C gave 2′,3′-*O*-isopropylideneuridine-5-acetic acid methyl ester (**3**) in 42% yield[10)] and successive de-

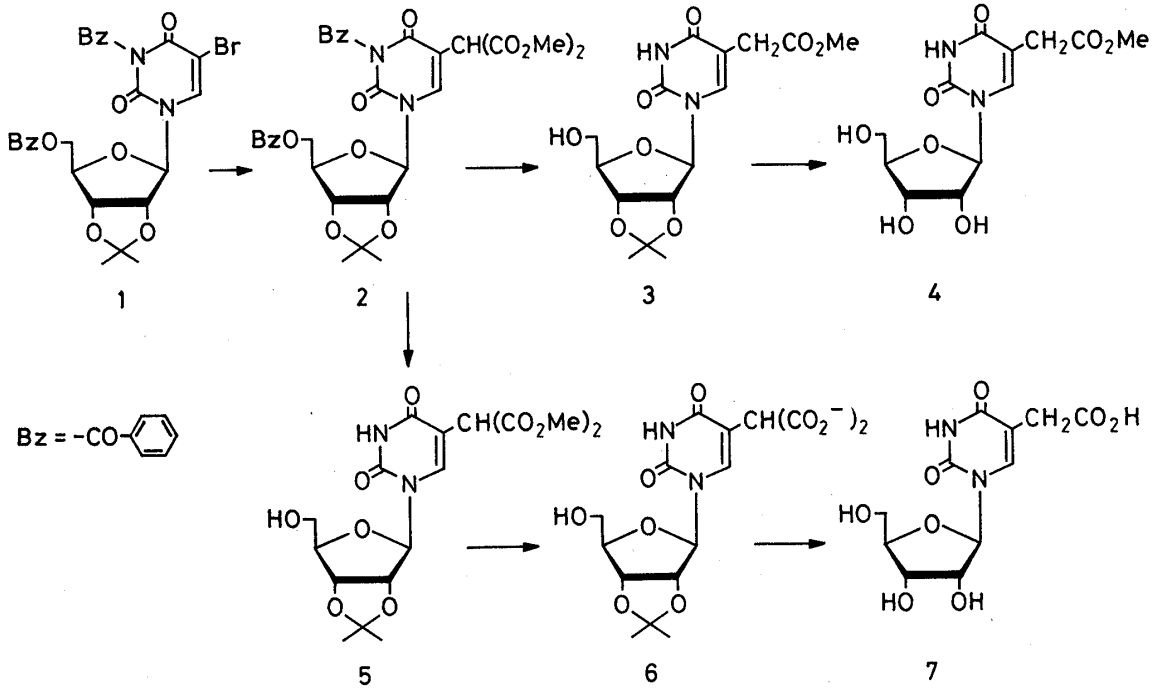

Chart 1

acetonation of **3** in 50% trifluoroacetic acid afforded the known uridine-5-acetic acid methyl ester (**4**)[11,12] in 84% yield. The structure of **4** was fully characterized [NMR, MS, ultraviolet (UV) absorption, and elemental analysis]. On the other hand, treatment of the foamy material (**2**) in methanolic sodium methoxide at room temperature gave a debenzoylated product (**5**) as crystals in 70% yield. Hydrolysis of **5** in 0.5 N NaOH at room temperature followed by treatment with 50% trifluoroacetic acid at 50 °C afforded uridine-5-acetic acid (**7**)[11] in 78% yield. Compounds **4** and **7**, which are minor nucleosides in transfer ribonucleic acids (tRNAs), have been synthesized by the condensation of a preformed uracil and an appropriate sugar,[11a] by chain elongation of 5-hydroxymethyluridines,[11b] and by the Wittig reaction of 5-hydroxyuridines.[12] The present synthesis has the following characteristics: the starting 5-bromouridine is easily accessible, reaction conditions for each step are mild, and the reaction sequences can be shortened.

A plausible mechanism for the formation of **2** is as follows (Chart 2). Nucleophilic attack of the carbanion of dimethyl malonate initially occurs at the C-6 position of **1** to give a 5,6-dihydro intermediate (A). Next, a carbanion, generated from the methine on the attached malonate and DBU, displaces bromine at C-5 to form a cyclopropane intermediate (B).[13] Finally, cleavage of the cyclopropane ring with participation by the lone pair of electrons on the N^1-atom results in the formation of **2**. The intermediacy of B and the route from B to **2** are supported by the findings that ethoxycarbonylcarbene adds to the 5,6-double bond of 1,3-dimethyluracil to give a cyclopropane derivative, which on heating under acidic conditions is converted to 1,3-dimethyluracil-5-acetic acid ethyl ester.[14,15] It should be noted that the present mechanism is different from the two previously proposed mechanisms[3,4] for 5-substituted uridine formation by other reagents.

We also investigated the reactions of **1** with other active methylene compounds such as nitromethane, nitroethane, and ethyl acetoacetate. However, in every case, they afforded a complex mixture of products and the only isolable product was an N^3-benzoyl-ribosylurea derivative (**9**). Such a compound is potentially useful as a precursor for the synthesis of a variety of nucleoside analogs.[16] Practical synthesis of **9** was performed by using N^3,5′-*O*-dibenzoyl-2′,3′-*O*-isopropylideneuridine (**8**), a bromine-free derivative of **1**. Treatment of **8**

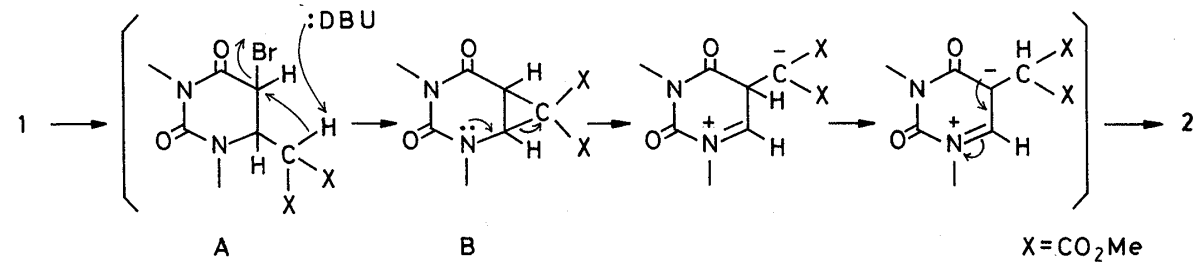

Chart 2

with ethyl acetoacetate (2 eq) in dry THF in the presence of DBU (1.5 eq) at room temperature overnight followed by silica gel chromatography of the products gave **9** in 70% yield, as crystals. The structure of **9** was indicated by the MS and elemental analysis ($C_{23}H_{24}N_2O_7$) and confirmed by the following analysis. The NMR spectrum showed two NH protons at 9.39 ppm (doublet, $J=7.6$ Hz) and 8.87 ppm (singlet) in addition to the ring protons of two benzoyl groups, sugar protons, and isopropylidene resonances. The UV spectrum showed λ_{max} at 230 nm ($\varepsilon=28000$) with weak absorption at 270 nm (shoulder, $\varepsilon=2300$).

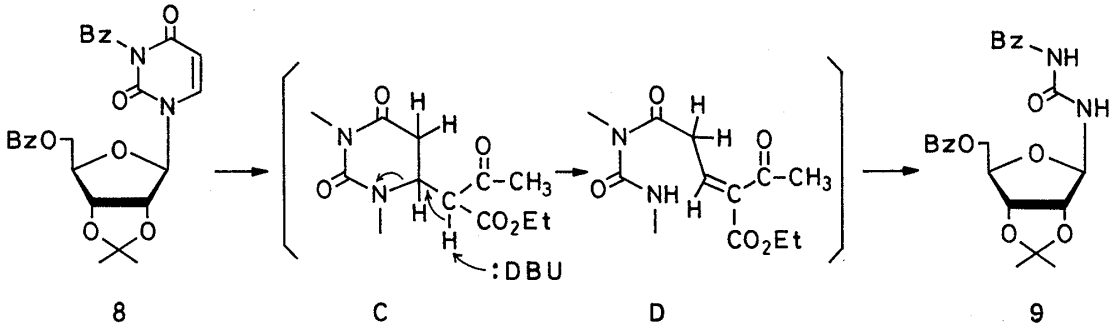

Chart 3

A possible mechanism of the formation of **9** is illustrated in Chart 3. Dissociation of the active methine proton of the initially formed intermediate (C) causes fission of the N^1–C^6 bond to give a ring-opened intermediate (D). Then, the carbonyl function at the 4-position undergoes intra- and/or intermolecular attack(s) by dissociated species derived from ethyl acetoacetate to afford **9** and fragment(s) containing the C^4–C^5–C^6 portion.[17]

As we have suggested in this paper, the formation of a 6-substituted uridine should be possible by the reaction of a 5-bromouridine with an active methylene compound. Our detailed study on this reaction will be reported in a forthcoming paper.

Experimental

Melting points were determined on a Yanagimoto MP-3 micro-melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL FX-100FT spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad). All exchangeable protons were confirmed by addition of D_2O. UV absorption spectra were recorded with a Shimadzu UV-240 spectrophotometer. MS were measured on a JEOL D-300 spectrometer. TLC and high-performance TLC (HPTLC) were carried out on E. Merck precoated Silica gel $60F_{254}$ plates (No. 5729 and 5628) by developing with $CHCl_3$–MeOH solutions or $CHCl_3$–AcOEt solutions. Silica gel for column chromatography was Wako-gel C-200. The starting nucleoside, uridine, was purchased from Yamasa Shoyu Co., Ltd.

***N*^{3},5′-*O*-Dibenzoyl-5-bromo-2′,3′-*O*-isopropylideneuridine (1)**——BzCl (13.9 ml, 115 mmol) was added in portions to an ice-cooled mixture of 5-bromo-2′,3′-*O*-isopropylideneuridine (19.0 g, 52.3 mmol), DMAP (1.28 g, 10.5 mmol) and Et_3N (16.9 ml, 120 mmol) in CH_2Cl_2 (200 ml). After being stirred at room temperature for 0.5 h, the

whole was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with H_2O, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallized from EtOH to give 28.4 g (94.9%) of **1**, mp 166—167 °C. UV λ_{max}^{MeOH} nm (ε): 280 sh (10300), 252 (18800), 230 (19400), λ_{max}^{MeOH} nm (ε): 242.5 (17200), 215.5 (15000). NMR ($CDCl_3$): 8.1—7.3 (10H, m, benzoyl protons), 7.75 (1H, s, 6-H), 5.72 (1H, d, 1′-H, $J_{1',2'}$ = 2.0 Hz), 5.06 (1H, dd, 2′-H, $J_{2',3'}$ = 6.4 Hz), 4.88 (1H, dd, 3′-H), 4.56 (3H, m, 4′,5′-H), 1.57, 1.36 (3H each, s, isopropyl-CH_3). MS *m/e*: 570, 572 (M^+). *Anal.* Calcd for $C_{26}H_{23}BrN_2O_8$: C, 54.65; H, 4.06; Br, 13.98; N, 4.90. Found: C, 54.45; H, 3.91; Br, 14.11; N, 4.95.

N^3,5′-*O*-Dibenzoyl-2′,3′-*O*-isopropylideneuridine-5-malonic Acid Dimethyl Ester (2)——Dimethyl malonate (1.8 ml, 15.3 mmol) and DBU (2.9 ml, 19.5 mmol) were added to a solution of **1** (8.0 g, 13.9 mmol) in dry THF (80 ml). The mixture was stirred at room temperature for 15 h and then neutralized with AcOH. TLC ($CHCl_3$–AcOEt, 4 : 1 v/v) showed a new spot at *Rf* 0.52 and a minor spot of **1** at *Rf* 0.60. After removal of the solvent *in vacuo*, the residue was partitioned between AcOEt and H_2O, then the organic layer was washed with H_2O, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography of the residue on a column of silica gel (240 g) with $CHCl_3$ as an eluent gave 7.8 g (95%) of **2** as a foam. UV λ_{max}^{MeOH} nm: 275 sh, 252.5, 236, λ_{min}^{MeOH} nm: 242, 216. NMR ($CDCl_3$): 8.2—7.3 (11H, m, 6-H and benzoyl protons), 5.69 (1H, d, 1′-H, $J_{1',2'}$ = 1 Hz), 5.17 (1H, dd, 2′-H, $J_{2',3'}$ = 6.3 Hz), 4.88 (1H, dd, 3′-H, $J_{3',4'}$ = 2.4 Hz), 4.77 (1H, s, $CH(CO_2Me)_2$), 4.53 (3H, m, 4′,5′-H), 3.75, 3.72 (3H each, s, CO_2CH_3), 1.57, 1.36 (3H each, s, isopropyl-CH_3). MS *m/e*: 607 ($M^+ - 15$). This was used for the next step without further purification.

2′,3′-*O*-Isopropylideneuridine-5-acetic Acid Methyl Ester (3)——A 2.2 N NaOMe–MeOH (12 ml) mixture was added to a solution of **2** (5.0 g, 8.0 mmol) in abs. MeOH (100 ml), and the whole was stirred at 50 °C for 40 h, neutralized by addition of Dowex 50W (H^+ form) resin, and filtered. The resin was washed with MeOH. The combined filtrates were evaporated and the residue was chromatographed on a column of silica gel (150 g). The eluate with $CHCl_3$ containing 2% MeOH was concentrated and the residue was crystallized from EtOH to give 1.2 g (42%) of **3**, mp 128—129 °C. UV λ_{max}^{MeOH} nm (ε): 263 (9900), λ_{min}^{MeOH} nm (ε): 231 (2200). NMR ($CDCl_3$): 9.37 (1H, br s, N^3-H), 7.54 (1H, s, 6-H), 5.65 (1H, d, 1′-H, $J_{1',2'}$ = 2.2 Hz), 5.00 (2H, m, 2′,3′-H), 4.33 (1H, m, 4′-H), 3.84 (3H, m, 5′-H and 5′-OH), 3.72 (3H, s, CO_2CH_3), 3.36 (2H, br s, CH_2CO_2Me), 1.58, 1.36 (3H each, s, isopropyl-CH_3). MS *m/e*: 356 (M^+). *Anal.* Calcd for $C_{15}H_{20}N_2O_8$: C, 50.56; H, 5.66; N, 7.86. Found: C, 50.31; H, 5.71; N, 7.77.

Uridine-5-acetic Acid Methyl Ester (4)——Compound **3** (0.5 g, 1.4 mmol) was dissolved in 50% aqueous CF_3CO_2H, then the solution was stirred at room temperature for 0.5 h and evaporated *in vacuo* to dryness. The residue was crystallized from MeOH–Et_2O to give 0.37 g (84%) of **4**, mp 165—166 °C (lit.[11a] mp 163—165 °C). UV $\lambda_{max}^{H_2O}$ nm (ε): 265 (9900), $\lambda_{min}^{H_2O}$ nm (ε): 232.5 (2200). NMR (DMSO-d_6): 11.46 (1H, s, N^3-H), 7.85 (1H, s, 6-H), 5.79 (1H, d, 1′-H, $J_{1',2'}$ = 4.9 Hz), 5.40 (1H, d, 2′-OH), 5.13 (2H, m, 3′,5′-OH), 4.1—3.7 (3H, m, 2′,3′,4′-H), 3.60 (5H, br s, 5′-H and CO_2CH_3), 3.27 (2H, s, CH_2CO_2Me). MS *m/e*: 316 (M^+). *Anal.* Calcd for $C_{12}H_{16}N_2O_8$: C, 45.57; H, 5.10; N, 8.86. Found: C, 45.25; H, 5.10; N, 8.94.

2′,3′-*O*-Isopropylideneuridine-5-malonic Acid Dimethyl Ester (5)——A 2 N NaOMe–MeOH (2.75 ml) mixture was added to a solution of **2** (1.4 g, 2.2 mmol) in abs. MeOH (10 ml) at room temperature. After being stirred for 0.5 h, the mixture was neutralized with Dowex 50W (H^+ form) resin and filtered. The resin was washed with MeOH and the combined filtrates were evaporated *in vacuo* to dryness. The residue was crystallized from EtOH to give 0.7 g (70%) of **5**, mp 164—165 °C. UV λ_{max}^{MeOH} nm (ε): 264 (9900), λ_{min}^{MeOH} nm (ε): 232.5 (2400). NMR ($CDCl_3$): 9.16 (1H, br s, N^3-H), 7.94 (1H, s, 6-H), 5.75 (1H, d, 1′-H, $J_{1',2'}$ = 1.7 Hz), 4.94 (3H, m, 2′,3′-H and $CH(CO_2Me)_2$), 4.44 (1H, br s, 4′-H), 3.89 (2H, m, 5′-H), 3.79, 3.78 (3H each, s, CO_2CH_3), 3.12 (1H, t, 5′-OH), 1.59, 1.37 (3H each, s, isopropyl-CH_3). MS *m/e*: 414 (M^+). *Anal.* Calcd for $C_{17}H_{22}N_2O_{10}$: C, 49.28; H, 5.35; N, 6.76. Found: C, 49.15; H, 5.29; N, 6.78.

Uridine-5-acetic Acid (7)——Compound **5** (0.5 g, 1.2 mmol) was dissolved in 0.5 N aqueous NaOH (12 ml). The solution was stirred at room temperature for 3 h, then neutralized by addition of Dowex 50W (H^+ form) resin. The mixture was filtered. The resin was washed with H_2O and the combined filtrates were evaporated *in vacuo*. Analysis of the residue by paper electrophoresis indicated the production of a 5-malonic acid (**6**). The data are summarized below. The residue was dissolved in 50% aqueous CF_3CO_2H (5 ml) and the solution was stirred at 50 °C for 4.5 h then evaporated to dryness. The resulting solid was crystallized from H_2O–EtOH to give 0.28 g (78%) of **7**, mp 230.5 °C (lit.[11a] mp 238—240 °C). UV $\lambda_{max}^{H_2O}$ nm (ε): 265.5 (9600), $\lambda_{min}^{H_2O}$ nm (ε): 233.5 (2300). NMR (DMSO-d_6): 12.31 (1H, br s, N^3-H), 11.41 (1H, s, CO_2H), 7.81 (1H, s, 6-H), 5.78 (1H, d, 1′-H, $J_{1',2'}$ = 4.9 Hz), 5.4 (1H, br, 2′-OH), 5.1 (2H, br, 3′,5′-OH), 4.1—3.7 (3H, m, 2′,3′,4′-H), 3.58 (2H, m, 5′-H), 3.16 (2H, s, CH_2CO_2H). The UV and NMR spectra were identical with those of an authentic sample provided by Dr. Ikeda.[11b] MS *m/e*: 302 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_2O_8$: C, 43.71; H, 4.67; N, 9.27. Found: C, 43.57; H, 4.61; N, 9.24. Mobility on paper electrophoresis (0.05 M triethylammonium bicarbonate buffer, pH 8.2, 700 volts, 40 min): +5.8 cm; compound **6**, +8.1 cm; 5′-uridylic acid, +8.3 cm; uridine, +3.7 cm.

N^3,5′-*O*-Dibenzoyl-2′,3′-*O*-isopropylideneuridine (8)——This compound was prepared from 2′,3′-*O*-isopropylideneuridine in the same manner as described above for **1**: yield 84%, mp 176.5—177 °C (from EtOH). UV λ_{max}^{MeOH} nm (ε): 251 (22200), 236 (20700), λ_{min}^{MeOH} nm (ε): 241.5 (19900), 216 (13500). NMR ($CDCl_3$): 8.1—7.3 (11H, m, 6-H and benzoyl protons), 5.73 (1H, d, H-5, $J_{5,6}$ = 8.3 Hz), 5.68 (1H, d, 1′-H, $J_{1',2'}$ = 1.5 Hz), 5.10 (1H, dd, 2′-H, $J_{2',3'}$ = 6.3 Hz), 4.88 (1H, br d, 3′-H), 4.52 (3H, br s, 4′,5′-H), 1.56, 1.35 (3H each, s, isopropyl-CH_3). MS *m/e*: 477 ($M^+ - 15$). *Anal.* Calcd for $C_{26}H_{24}N_2O_8$: C, 63.41; H, 4.91; N, 5.69. Found: C, 63.18; H, 4.90; N, 5.69.

N^3-Benzoyl-N^1-(5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)urea (9)——Ethyl acetoacetate (2.5 ml,

20 mmol) and DBU (2.3 ml, 15.3 mmol) were added to a solution of **8** (5.0 g, 10.2 mmol) in THF (50 ml). The mixture was stirred under an argon atmosphere overnight at room temperature and neutralized with AcOH. After removal of the solvent *in vacuo*, the residue was partitioned between AcOEt and H_2O, then the organic layer was washed with H_2O, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel (150 g) with $CHCl_3$ as an eluent, and appropriate fractions were pooled and concentrated to dryness. The residue was crystallized from EtOH to give 3.14 g (70%) of **9**, mp 167—169 °C. UV λ_{max}^{MeOH} nm (ε): 270 sh (2300), 230 (28000), λ_{min}^{MeOH} nm (ε): 211.5 (12800). NMR ($CDCl_3$): 9.39 (1H, br d, N^1-H, $J_{N^1,1'}=7.6$ Hz), 8.87 (1H, br s, N^3-H), 8.1—7.3 (10H, m, benzoyl protons), 5.70 (1H, br d, 1′-H), 4.85 (2H, s, 2′,3′-H), 4.50 (3H, s, 4′,5′-H), 1.59, 1.38 (3H each, s isopropyl-CH_3). MS *m/e*: 425 (M^+-15). *Anal.* Calcd for $C_{23}H_{24}N_2O_7$: C, 62.72; H, 5.49; N, 6.36. Found: C, 62.54; H, 5.38; N, 6.43. HPTLC ($CHCl_3$–AcOEt, 4:1 v/v): *Rf* 0.26 (*Rf* 0.29 for compound **8**).

Reaction of 1 with Nitroethane in the Presence of DBU——Nitroethane (42 μl, 0.58 mmol) and DBU (120 μl, 0.8 mmol) were added to a solution of **1** (300 mg, 0.53 mmol) in dry THF (3 ml). The mixture was stirred overnight at room temperature and then neutralized with AcOH. TLC ($CHCl_3$–AcOEt, 4:1 v/v) analysis showed that the reaction gave a complex mixture of products. After work-up similar to that described above for **9** and column chromatography (silica gel, 15 g), 28 mg (12%) of **9** was obtained as crystals (mp 166—168 °C). Similar treatment of **1** with nitromethane or ethyl acetoacetate gave **9** in low yield.

Acknowledgement This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan. The instrumental analyses were performed by the staff of the Center of Instrumental Analysis, Hokkaido University, to whom our thanks are due. We are grateful to Dr. Kazuyoshi Ikeda of the same institute for providing an authentic sample of uridine-5-acetic acid.

References and Notes

1) This paper constitutes Part LXX of "Nucleosides and Nucleotides." Part LXIX: M. Sato, A. Ono, H. Higuchi, and T. Ueda, *Nucleic Acids Res.*, **14**, 1405 (1986).
2) For reviews, see *a*) T. K. Bradshaw and D. W. Hutchinson, *Chem. Soc. Rev.*, **6**, 43 (1977); *b*) D. E. Bergstrom, *Nucleosides & Nucleotides*, **1**, 1 (1982).
3) *a*) H. Inoue and T. Ueda, *Chem. Pharm. Bull.*, **19**, 1743 (1971), *idem, ibid.*, **26**, 2657 (1978); *b*) T. Ueda, H. Inoue, and A. Matsuda, *Ann. N. Y. Acad. Sci.*, **255**, 121 (1975).
4) H. Inoue, S. Tomita, and T. Ueda, *Chem. Pharm. Bull.*, **23**, 2614 (1975).
5) A. Matsuda, H. Inoue, and T. Ueda, *Chem. Pharm. Bull.*, **26**, 2340 (1978).
6) A. Rosenthal and R. H. Dodd, *Carbohydr. Res.*, **85**, 15 (1980).
7) T. Sano, H. Inoue, and T. Ueda, *Chem. Pharm. Bull.*, **33**, 3595 (1985).
8) For the structural assignment of N^3-acylated uridines, see T. Kamimura, T. Masegi, M. Sekine, and T. Hata, *Tetrahedron Lett.*, **25**, 4241 (1984).
9) In the absence of an N^3-protecting group, no reaction occurred under similar conditions, even after 48 h.
10) Optimal reaction conditions have not been established.
11) *a*) J. D. Fissekis and F. Sweet, *Biochemistry*, **9**, 3136 (1970); *b*) K. Ikeda, S. Tanaka, and Y. Mizuno, *Chem. Pharm. Bull.*, **23**, 2958 (1975).
12) K. Hirota, M. Suematsu, Y. Kuwabara, T. Asao, and S. Senda, *J. Chem. Soc., Chem. Commun.*, **1981**, 623.
13) For the reaction of α-bromo-α,β-unsaturated carbonyl compounds with malonate esters giving cyclopropanes, see *a*) M. Kocór, W. Kroszczyński, and J. Pietrzak, *Synthesis*, **1980**, 742; *b*) H. Takei, Y. Fukuda, K. Sugaya, T. Taguchi, and T. Kawara, *Chem. Lett.*, **1980**, 1307.
14) H. P. M. Thiellier, G. J. Koomen, and U. K. Pandit, *Tetrahedron*, **33**, 1493 (1977).
15) In the present case, cyclopropane ring-opening of B may occur without an acid catalyst; the fission would result in the formation of a carbanion stabilized by two X groups. However, a 5,6-dihydro-5,6-dimalonate intermediate, which may be produced by the intermolecular substitution of A with dimethyl malonate carbanion, can not be excluded as an alternative intermediate in the formation of **2**.
16) E. Stankevich, A. Dreimane, E. Liepinš, A. Kemme, and J. Bleidelis, *Nucleosides & Nucleotides*, **2**, 155 (1983).
17) Analogous reactions have appeared in the chemistry of pyrimidines: *a*) K. Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **46**, 846 (1981); *b*) T.-L. Su, K. A. Watanabe, and J. J. Fox, *Tetrahedron*, **38**, 1405 (1982).