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Pyrimidine Derivatives and Related Compounds. XLIX.[1] Reaction of Anhydrouridines with the Vilsmeier Reagent

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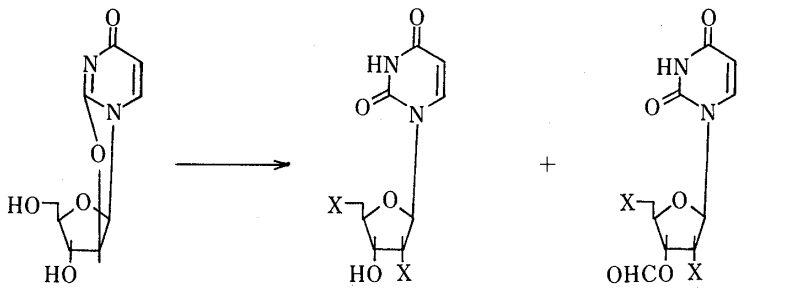
Treatment of O^2,2′-anhydrouridine (**1**) with phosphorus oxychloride in dimethylformamide (DMF) at 60 °C afforded both 2′,5′-dichloro-2′,5′-dideoxyuridine (**2a**) and 2′,5′-dichloro-2′,5′-dideoxy-3′-*O*-formyluridine (**3a**). The reaction of **1** with phosphorus oxybromide in DMF gave the corresponding 2′,5′-dibromo derivatives (**2b**) and (**3b**). O^2,5′-Anhydro-2′,3′-*O*-isopropylideneuridine (**4**) was treated with the Vilsmeier reagent (DMF/POX_3) to give the corresponding 5′-halogeno-5′-deoxy-2′,3′-*O*-isopropylideneuridines (**5a** and **5b**) in high yields. Under the same conditions, the reaction of 6,5′-cyclo-2′,3′-*O*-isopropylideneuridine (**6**) with the Vilsmeier reagent (DMF/POX_3) afforded the corresponding 1-(5-halogeno-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-dimethylaminomethylenebarbituric acids (**7a** and **7b**) in high yields.

Keywords——anhydrouridine; Vilsmeier reagent; 2′,5′-dihalogenouridine; phosphorus oxychloride; phosphorus oxybromide

5-Substituted pyrimidine nucleosides have potential application as antiviral agents and in the treatment of tumors. Of particular interest are agents to inhibit thymidylate synthetase.[2] 5-Formyluridine derivatives are considered to be useful intermediates for the synthesis of 5-substituted uridine derivatives. However, conventional procedures for the preparation of 5-formyluridines involve tedious steps.[3] Previously, we reported that the reaction of 1,3-disubstituted uracil with the Vilsmeier reagent afforded the corresponding 5-formyluracils.[4] This procedure cannot be applied to uracils containing dissociable protons, such as 3-unsubstituted uridine derivatives.[5] In fact, treatment of 1-methyluracil with the Vilsmeier reagent under the same conditions as reported previously[4] resulted in the recovery of the starting material. With the aim of developing a simple preparation of 5-formyluridines, an anhydrouridine containing no dissociable proton was allowed to react with the Vilsmeier reagent. Although the expected 5-formyluridine derivative could not be obtained, we found that the counter anion of the Vilsmeier reagent reacted as a nucleophile.

O^2,2′-Anhydrouridine (**1**) has no dissociable proton at the N_3-position of the pyrimidine ring, and therefore, the reaction of **1** with the Vilsmeier reagent was carried out first. Thus, treatment of **1** with phosphorus oxychloride (1.2 eq) in dimethylformamide (DMF) at 60 °C for 2 h did not give the expected 5-formyluridine but 2′,5′-dichloro-2′,5′-dideoxyuridine (**2a**) and 2′,5′-dichloro-2′,5′-dideoxy-3′-*O*-formyluridine (**3a**) were obtained in 39 and 55% yields, respectively. The dichlorouridine (**2a**) was identical with an authentic sample.[6] The structure of the 3′-formyl derivative (**3a**) was determined from the following experimental results. Thus, compound **3a** was also obtained in high yield by treatment of **2a** with the Vilsmeier reagent (DMF–$POCl_3$). Compound **3a** was quantitatively converted into **2a** by boiling in methanol. Analogous treatment of **1** with phosphorus oxybromide instead of $POCl_3$ in DMF afforded both 2′,5′-dibromo derivatives (**2b**) and (**3b**) in 68 and 20% yields, respectively.

A plausible mechanism for the formation of **2** and **3** is as follows. The anhydronucleoside (**1**) undergoes cleavage of the O^2,2′-anhydro ring by nucleophilic attack of the halide ion (X^-)

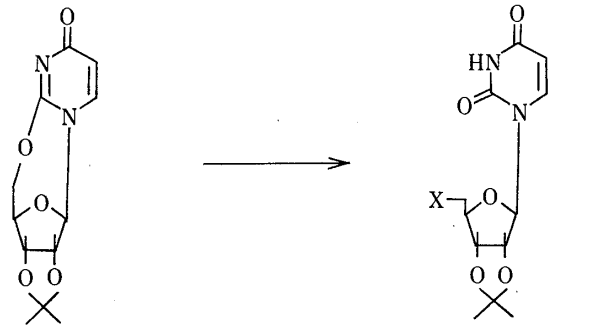


1

2a : X=Cl
2b : X=Br

3a : X=Cl
3b : X=Br

Chart 1



4

5a : X=Cl
5b : X=Br

Chart 2

and halogenation of the 5′-hydroxyl group as described previously[7] to yield the 2′,5′-dihalogenated nucleosides (**2**) and (**3**).

When O^2,5′-anhydro-2′,3′-*O*-isopropylideneuridine (**4**) was treated with the Vilsmeier reagent (DMF–$POCl_3$), the known 5′-chloro-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**5a**)[7] was formed in 78% yield. Compound **5a** was also obtained in 78% yield by the reaction of 2′,3′-*O*-isopropylideneuridine with DMF–$POCl_3$. Similar treatment of **4** with $POBr_3$ gave the 5′-bromo derivative (**5b**)[7] (94%), which was also obtained from 2′,3′-*O*-isopropylideneuridine in 82% yield.

On the other hand, the reaction of 6,5′-cyclo-2′,3′-*O*-isopropylideneuridine (**6**) containing a dissociable proton with the Vilsmeier reagent (DMF–$POCl_3$) gave 1-(5-chloro-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-dimethylaminomethylenebarbituric acid (**7a**) in 81% yield. The use of $POBr_3$ resulted in the formation of the 5′-bromo derivative (**7b**) in 83% yield. The structures of **7a** and **7b** were supported by microanalytical and spectral data. Confirmation of the structure of **7a** rests upon its conversion into 1-(5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-dimethylaminomethylenebarbituric acid (**9**). Thus, on heating a mixture of **7a** and sodium benzoate in methanol, the 5′-benzoyl derivative (**9**) was obtained in 50% yield. Compound **9** was identical with an authentic sample prepared by the reaction[4] of 1-(5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)barbituric acid (**8**)[8] with the Vilsmeier reagent (DMF–$POCl_3$).

A possible reaction sequence for the formation of **7** involves an initial nucleophilic attack of the halide ion (X^-) at the 5′-position of **6** to give a barbituric acid intermediate A, as outlined in Chart 4.

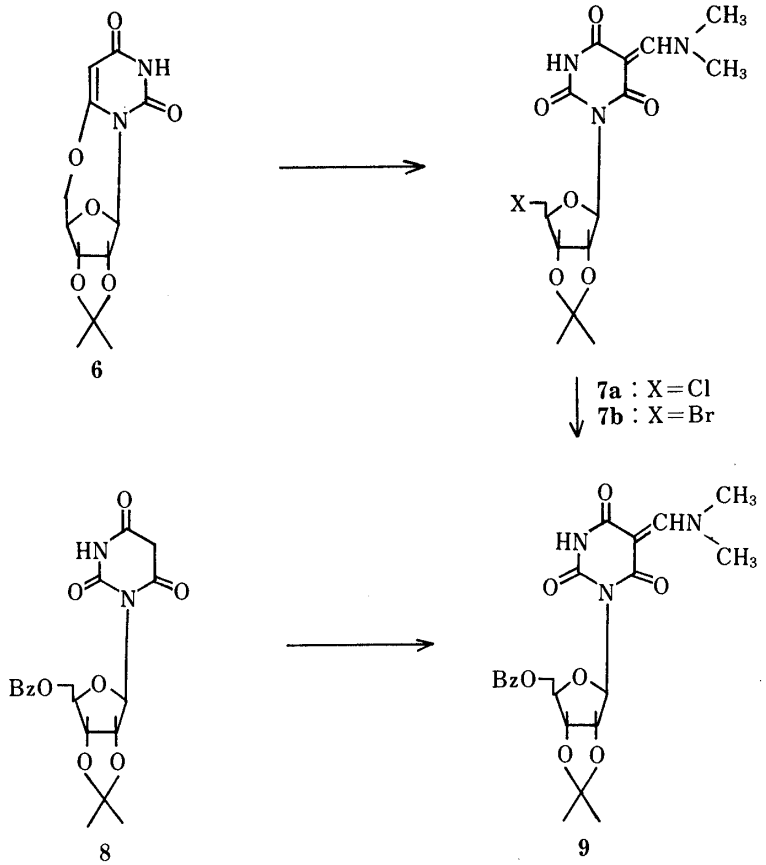


Chart 3

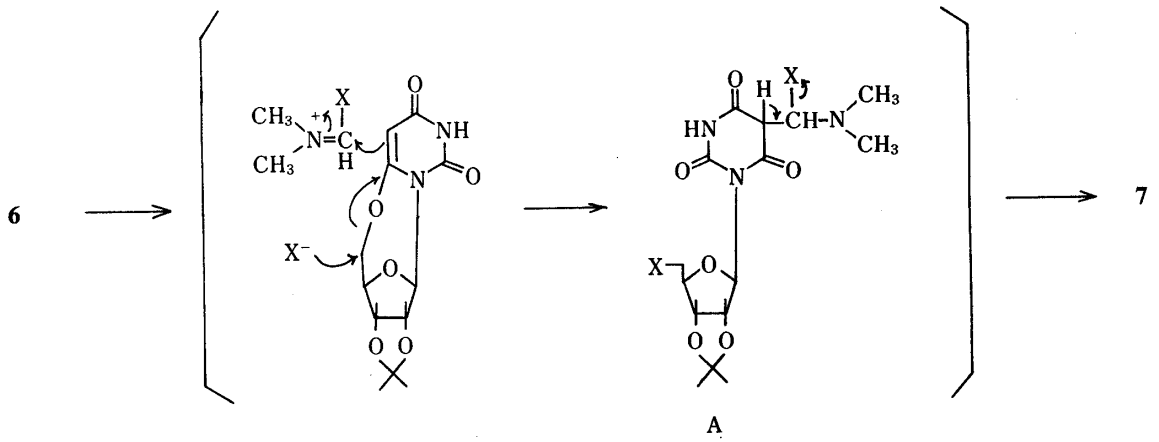


Chart 4

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (NMR) were recorded on a JEOL JNM-PS-100 nuclear magnetic resonance spectrometer with tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million (s=singlet, d=doublet, dd=doublet of doublets, m=multiplet, br=broad). Ultraviolet (UV) spectra were measured on a Hitachi 323 spectrophotometer. Mass spectra (MS) were taken on a JEOL JMS-D300 machine operating at 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory of our university.

2′,5′-Dichloro-2′,5′-dideoxyuridine (2a) and 2′,5′-Dichloro-2′,5′-dideoxy-3′-*O*-formyluridine (3a)——Phosphorus oxychloride (0.368 g, 0.0024 mol) was dissolved in dry DMF (30 ml) at below 5 °C, then 0.452 g (0.002 mol) of **1** was added to the solution. The mixture was heated at 60 °C for 2 h and dissolved in cold water. The aqueous solution was

extracted with chloroform and the extract was dried with sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with chloroform. The early-eluting fraction gave 0.33 g (55%) of **3a**, mp 189—190 °C. UV λ_{max}^{EtOH} nm (ε): 258 (9.2×10^3). NMR (DMSO-d_6) δ: 3.97 (2H, m), 4.42 (1H, m), 4.52 (1H, dd, $J=7$, 3 Hz), 5.10 (1H, m), 5.80 (1H, dd, $J=8$, 2 Hz), 6.09 (1H, d, $J=7$ Hz), 7.76 (1H, d, $J=8$ Hz), 8.45 (1H, s), 11.55 (1H, br). MS *m/e*: 292 (M^+). *Anal.* Calcd for $C_{10}H_{10}Cl_2N_2O_5$: C, 38.85; H, 3.26; N, 9.06, Found: C, 38.59; H, 3.29; N, 9.08. The later-eluting fraction gave 0.22 g (39%) of **2a**, mp 159—160 °C (lit.[6] 159—161 °C). UV λ_{max}^{EtOH} nm (ε): 258 (9.7×10^3). NMR (DMSO-d_6) δ: 3.96 (2H, br), 4.21 (2H, br), 4.76 (1H, m), 5.77 (1H, dd, $J=8$, 2 Hz), 6.11 (1H, d, $J=7$ Hz), 6.18 (1H, br), 7.71 (1H, d, $J=7$ Hz), 11.41 (1H, br). MS *m/e*: 280 (M^+). *Anal.* Calcd for $C_9H_{10}Cl_2N_2O_4$: C, 38.45; H, 3.59; N, 9.97. Found: C, 38.66; H, 3.64; N, 10.11.

Conversion of 2a to 3a——Phosphorus oxychloride (0.184 g, 0.0012 mol) was dissolved in dry DMF (15 ml) at below 5 °C, then **2a** (0.281 g, 0.001 mol) was added to the solution. The mixture was heated at 60 °C for 2 h and dissolved in cold water. The solution was extracted with chloroform and the extract was dried with sodium sulfate. The solvent was removed under reduced pressure to give 0.278 g (95%) of **3a**, which was identical with the sample obtained above.

Conversion of 3a to 2a——The 3′-*O*-formyluridine (**2a**) (0.293 g, 0.001 mol) was refluxed in methanol (30 ml) for 8 h. The solvent was removed under reduced pressure to give 0.273 g (97%) of **2a**, which was identical with the sample obtained above.

2′,5′-Dibromo-2′,5′-dideoxyuridine (2b) and 2′,5′-Dibromo-2′,5′-dideoxy-3′-*O*-formyluridine (3b)——Phosphorus oxybromide (0.683 g, 0.0024 mol) was dissolved in dry DMF (30 ml) at below 5 °C, then 0.452 g (0.002 mol) of **1** was added to the solution. The mixture was heated at 60 °C for 2 h and dissolved in cold water. The aqueous solution was extracted with chloroform and the extract was dried with sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with chloroform. The early-eluting fraction gave 0.153 g (20%) of **3b**, mp 195—197 °C. UV λ_{max}^{EtOH} nm (ε): 258 (9.6×10^3). NMR (DMSO-d_6) δ: 3.79 (2H, m), 4.37 (1H, m), 5.06 (1H, m), 5.41 (1H, dd, $J=5$, 2 Hz), 5.77 (1H, dd, $J=8$, 2 Hz), 6.14 (1H, d, $J=8$ Hz), 7.74 (1H, d, $J=8$ Hz), 8.42 (1H, s), 11.53 (1H, br). MS *m/e*: 380 (M^+). *Anal.* Calcd for $C_{10}H_{10}Br_2N_2O_5$: C, 30.19; H, 2.53; N, 7.04. Found: C, 30.04; H, 2.55; N, 6.80. The later-eluting fraction gave 0.504 g (68%) of **2b**, mp 182—184 °C. UV λ_{max}^{EtOH} nm (ε): 258 (9.6×10^3). NMR (DMSO-d_6) δ: 3.75 (2H, m), 4.08 (2H, m), 4.73 (1H, dd, $J=8$, 5 Hz), 5.75 (1H, dd, $J=8$, 2 Hz), 6.14 (1H, d, $J=8$ Hz), 6.18 (1H, br), 7.66 (1H, d, $J=8$ Hz), 11.47 (1H, br). MS *m/e*: 368 (M^+). *Anal.* Calcd for $C_9H_{10}Br_2N_2O_4$: C, 29.22; H, 2.72; N, 7.57. Found: C, 29.20; H, 2.65; N, 7.59.

5′-Chloro-5′-deoxy-2′,3′-*O*-isopropylideneuridine (5a)——a) Phosphorus oxychloride (0.368 g, 0.0024 mol) was dissolved in dry DMF (30 ml) at below 5 °C, then 0.533 g (0.002 mol) of **4** was added to the solution. The mixture was heated at 60 °C for 2 h and dissolved in cold water. The aqueous solution was extracted with chloroform and the extract was dried with sodium sulfate. The solvent was removed under reduced pressure. Recrystallization from ethanol gave 0.47 g (78%) of **5a**, mp 182—183 °C (lit.[7] 173.5—177.5 °C). UV λ_{max}^{EtOH} nm (ε): 259 (9.9×10^3). NMR (DMSO-d_6) δ: 1.33 (3H, s), 1.52 (3H, s), 3.79 (2H, m), 4.18 (1H, m), 4.78 (1H, dd, $J=7$, 4 Hz), 5.06 (1H, dd, $J=7$, 3 Hz), 5.65 (1H, dd, $J=8$, 2 Hz), 5.79 (1H, d, $J=3$ Hz), 7.70 (1H, d, $J=8$ Hz), 11.37 (1H, m). MS *m/e*: 302 (M^+). *Anal.* Calcd for $C_{12}H_{15}ClN_2O_5$: C, 47.61; H, 4.99; N, 9.25. Found: C, 47.43; H, 5.13; N, 9.18.

b) Phosphorus oxychloride (0.368 g, 0.0024 mol) was dissolved in dry DMF (30 ml) at below 5 °C, then 0.569 g (0.002 mol) of 2′,3′-*O*-isopropylideneuridine was added to the solution. The mixture was heated at 60 °C for 2 h. The solution was treated as described above to give 0.47 g (78%) of **5a**.

5′-Bromo-5′-deoxy-2′,3′-*O*-isopropylideneuridine (5b)——a) Phosphorus oxybromide (0.683 g, 0.0024 mol) was dissolved in dry DMF (30 ml) at below 5 °C, then 0.533 g (0.002 mol) of **4** was added to the solution. The mixture was heated at 60 °C for 2 h and dissolved in cold water. The aqueous solution was extracted with chloroform and the extract was dried with sodium sulfate. The solution was removed under reduced pressure. Recrystallization from $CHCl_3$–hexane gave 0.65 g (94%) of **5b**, mp 185—187 °C (lit.[7] 179—181 °C). UV λ_{max}^{EtOH} nm (ε): 259 (9.7×10^3). NMR (DMSO-d_6) δ: 1.30 (3H, s), 1.49 (3H, s), 3.68 (2H, m), 4.19 (1H, m), 4.78 (1H, dd, $J=7$, 4 Hz), 5.08 (1H, dd, $J=7$, 2 Hz), 5.64 (1H, dd, $J=8$, 3 Hz), 6.81 (1H, d, $J=2$ Hz), 7.72 (1H, d, $J=8$ Hz), 11.39 (1H, br). MS *m/e*: 346 (M^+). *Anal.* Calcd for $C_{12}H_{15}BrN_2O_5$: C, 41.52; H, 4.36; N, 8.07. Found: C, 41.50; H, 4.32; N, 8.09.

b) Phosphorus oxybromide (0.683 g, 0.0024 mol) was dissolved in dry DMF (30 ml) at below 5 °C, then 0.569 g (0.002 mol) of 2′,3′-*O*-isopropylideneuridine was added to the solution. The mixture was heated at 60 °C for 2 h. The solution was treated as described above to give 0.57 g (82%) of **5b**.

1-(5-Chloro-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-dimethylaminomethylenebarbituric Acid (7a)——Phosphorus oxychloride (0.368 g, 0.0024 mol) was dissolved in dry DMF (30 ml) at below 5 °C, then 0.565 g (0.002 mol) of **6** was added to the solution. The mixture was heated at 60 °C for 2 h and dissolved in cold water. The aqueous solution was extracted with chloroform and the extract was dried with sodium sulfate. The solvent was removed under reduced pressure to give 0.606 g (81%) of **7a**, mp 204—205 °C. UV λ_{max}^{EtOH} nm (ε): 239 (7×10^3), 285 (sh) (7×10^3), 313 (12.8×10^3). NMR (DMSO-d_6) δ: 1.29 (3H, s), 1.48 (3H, s), 3.26 (3H, s), 3.47 (3H, s), 3.72 (2H, m), 4.03 (1H, m), 4.82 (1H, m), 5.11 (1H, dd, $J=7$, 1 Hz), 6.35 (1H, br), 8.12 (1H, s), 10.68 (1H, br). MS *m/e*: 372 (M^+). *Anal.* Calcd for $C_{15}H_{20}ClN_3O_6$: C, 48.20; H, 5.39; N, 11.24. Found: C, 48.11; H, 5.52; N, 11.06.

1-(5-Bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-dimethylaminomethylenebarbituric Acid (7b)——

Phosphorus oxybromide (0.683 g, 0.0024 mol) was dissolved in dry DMF (30 ml) at below 5 °C, then 0.565 g (0.002 mol) of **6** was added to the solution. The mixture was heated at 60 °C for 2 h and dissolved in cold water. The aqueous solution was extracted with chloroform and the extract was dried with sodium sulfate. The solvent was removed under reduced pressure to give 0.696 g (83%) of **7b**, mp 209—211 °C. UV λ_{max}^{EtOH} nm (ε): 240 (7.2×10^3), 285 (7.5×10^3), 313 (12.4×10^3). NMR (DMSO-d_6) δ: 1.31 (3H, s), 1.50 (3H, s), 3.27 (3H, s), 3.48 (3H, s), 3.65 (2H, m), 4.17 (1H, m), 4.86 (1H, m), 5.16 (1H, dd, $J=7$, 1 Hz), 6.39 (1H, br), 8.17 (1H, s), 10.73 (1H, br). MS *m/e*: 417 (M^+). *Anal.* Calcd for $C_{15}H_{20}BrN_3O_6$: C, 43.08; H, 4.82; N, 10.05. Found: C, 42.80; H, 4.80; N, 9.85.

1-(5-*O*-Benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-dimethylaminomethylenebarbituric Acid (9)——a) A mixture of **7a** (0.373 g, 0.001 mol) and sodium benzoate (0.216 g, 0.0015 mol) in methanol (10 ml) was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water. The solution was extracted with chloroform and the extract was dried with sodium sulfate. The solvent was removed under reduced pressure to give 0.23 g (50%) of **9**, mp 211—213 °C. UV λ_{max}^{EtOH} nm (ε): 226 (26.2×10^3), 314 (21.9×10^3). NMR (DMSO-d_6) δ: 1.37 (3H, s), 1.57 (3H, s), 3.38 (3H, s), 3.42 (3H, s), 4.50 (3H, m), 5.11 (2H, m), 6.59 (1H, s), 7.38—8.16 (5H, m), 9.51 (1H, br). MS *m/e*: 459 (M^+). *Anal.* Calcd for $C_{22}H_{25}N_3O_8$: C, 57.51; H, 5.48; N, 9.15. Found: C, 57.61; H, 5.50; N, 9.08.

b) Phosphorus oxychloride (0.23 g, 0.0015 mol) and dry DMF (0.11 g, 0.0015 mol) were dissolved in dry benzene (15 mol), then 0.404 g (0.001 mol) of **8**[8] was added to the solution. The mixture was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water. The solution was extracted with chloroform and the extract was dried with sodium sulfate. The solvent was removed under reduced pressure to give 0.37 g (80%) of **9**, which was identical with the sample obtained above.

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References and Notes

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