

H, m), 5.78 (1 H, br s), 7.5 (5 H, s); IR 1580, 1300, 1130  $\text{cm}^{-1}$ ; MS  $m/z$  240 ( $\text{M}^+$ ), 175, 174, 147.

5-Methyl-3-(trimethylsilyl)-3-sulfolene (**3i**):  $^1\text{H}$  NMR  $\delta$  0.13 (9 H, s), 1.39 (3 H, d,  $J = 7.0$  Hz), 3.71 (3 H, m), 6.08 (1 H, br s); IR 1590, 1300, 1240  $\text{cm}^{-1}$ ; MS  $m/z$  204 ( $\text{M}^+$ ), 140, 125, 73. Anal. Calcd for  $\text{C}_8\text{H}_{16}\text{O}_2\text{SSi}$ : C, 47.05; H, 7.84. Found: C, 46.6; H, 7.92. A minor product found in the reaction mixture was the isomer of **3i**, 2-methyl-4-(trimethylsilyl)-4,5-dihydrothiophene 1,1-dioxide (**5i**):  $^1\text{H}$  NMR  $\delta$  0.12 (9 H, s), 2.0 (3 H, br s), 2.31 (1 H, m), 2.95 (1 H, dd,  $J = 14, 5$  Hz), 3.35 (1 H, dd,  $J = 14, 9$  Hz), 6.20 (1 H, m). Also, the thermolysis of **3i** on a preparative GC (Carbowax column, injection port temperature 180  $^\circ\text{C}$ , oven temperature 70  $^\circ\text{C}$ ) gave 2-(trimethylsilyl)-1,3-pentadiene:  $^1\text{H}$  NMR  $\delta$  0.15 (9 H, s), 1.75 (3 H, d,  $J = 5$  Hz), 5.28 (1 H, d,  $J = 3.8$  Hz), 5.85 (1 H, dq,  $J = 5, 16$  Hz), 6.21 (1 H, d,  $J = 16$  Hz); MS  $m/z$  140 ( $\text{M}^+$ ), 125, 73.

3-Carbomethoxy-3-methyl-2,3-dihydrothiophene 1,1-dioxide:  $^1\text{H}$  NMR  $\delta$  1.58 (3 H, s), 3.08 (1 H, d,  $J = 14$  Hz), 3.75 (3 H, s), 3.82 (1 H, d,  $J = 14$  Hz), 6.56 (1 H, d,  $J = 6.0$  Hz), 6.75 (1 H, d,  $J = 6.0$  Hz); IR 3080, 1745, 1315, 1270, 1110  $\text{cm}^{-1}$ ; MS 131 ( $\text{M}^+ - \text{COOCH}_3$ ), 115, 103. Anal. Calcd for  $\text{C}_7\text{H}_{10}\text{O}_4\text{S}$ : C, 44.20; H, 5.30. Found: C, 43.9; H, 5.3.

**Acknowledgment.** We thank Dr. T. S. Chou for helpful discussion, and we also thank National Science Foundation of Republic of China for partial financial support.

**Registry No.** **1a**, 1193-10-8; **1b**, 62157-91-9; **1c**, 62157-92-0; **1d**, 62157-93-1; **1e**, 7311-87-7; **1f**, 104664-70-2; **1g**, 57465-40-4; **1h**, 64741-13-5; **1i**, 104692-94-6; **1j**, 67488-50-0; **2a**, 10033-87-1; **2b**, 104664-71-3; **2c**, 104664-72-4; **2d**, 104664-73-5; **2e**, 104664-74-6; **2f**, 104664-75-7; **2g**, 104664-76-8; **2h**, 104664-77-9; **2i**, 104664-78-0; **2j**, 104664-79-1; **2k**, 104664-80-4; **2l**, 104664-81-5; **2m**, 104664-82-6; **2n**, 104664-83-7; **2o**, 104664-84-8; **2p**, 104664-85-9; **2q**, 104664-86-0; **2r**, 104664-87-1; **2s**, 104664-88-2; **2t**, 104664-89-3; **2u**, 104664-90-6; **2v**, 104664-91-7; 2-(trimethylsilyl)-1,3-pentadiene, 29943-00-8; 3-carbomethoxy-3-methyl-2,3-dihydrothiophene 1,1-dioxide, 104664-92-8; methyl iodide, 74-88-4.

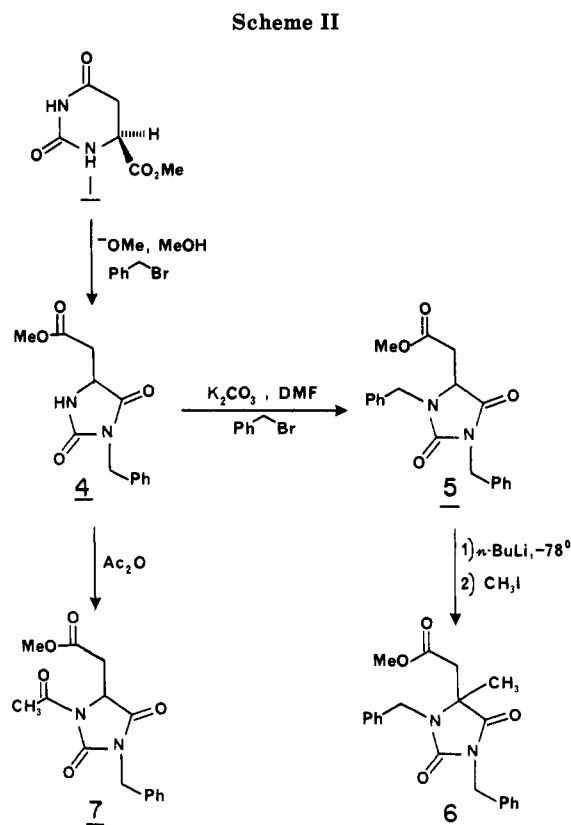
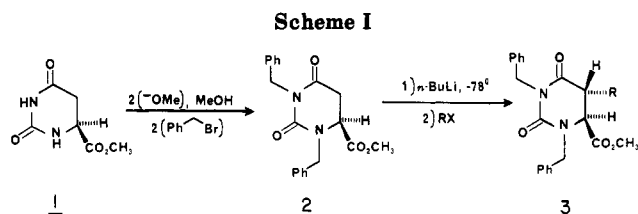
### Methoxide-Catalyzed Rearrangement of Methyl (*S*)-Dihydroorotate to Methyl Hydantoin-5-acetate

Loren D. Keys, III,<sup>†</sup> Kirsten Folting,<sup>§</sup> William E. Streib,<sup>§</sup> and Michael Johnston\*<sup>†</sup>

Departments of Chemistry and of Biochemistry and Molecular Biology, Searle Chemistry Laboratory, University of Chicago, Chicago, Illinois 60637, and the Molecular Structure Center, Department of Chemistry, University of Indiana, Bloomington, Indiana 47405

Received April 14, 1986

We required, in connection with our studies of the dihydroorotate dehydrogenases,<sup>1</sup> a method for preparation of *trans*-5-alkylated-6(*S*)-dihydroorotates, such as **3**. The only previous synthesis of this type of compound is that provided by Heidelberger and colleagues,<sup>2</sup> who showed that 1,3-dibenzyl and 1,3-dibenzyloxymethyl uracils and related pyrimidines can be reductively alkylated at C5 using lithium (tri-*sec*-butyl)borohydride (L-Selectride, Aldrich) and an alkylating agent. This method, applied to a 1,3-diprotected orotate, would at best afford the pair of 5*R*,6*S* and 5*S*,6*R* isomers of **3**. A plausible entry into the series providing only the 5*R*,6*S* compounds appeared to be by way of diastereospecific alkylation of a suitably 1,3-diprotected-(*S*)-dihydroorotate ester, such as **2**. During attempts to benzylate dihydroorotate **1** at N-3, we dis-



covered that sodium methoxide in methanol readily converts **1** to methyl hydantoin-5-acetate (**10**) in an apparently irreversible reaction. Using this rearrangement, we prepared methyl 1,3-dibenzylhydantoin-5-acetate (**5**), which undergoes alkylation at position 5 of the hydantoin ring.

### Results and Discussion

Methyl (*S*)-dihydroorotate (**1**) was prepared from (*S*)-dihydroorotic acid by reaction with diazomethane.<sup>3</sup> We chose to initiate our preparation of **3** by the stepwise protection of the amide nitrogens of the dihydroorotate ester. Thus, **1** was treated with 1 equiv of sodium methoxide and then reacted with benzyl bromide under refluxing conditions. This gave a monobenzylated product later confirmed to be the hydantoin **4**; a monobenzyl dihydroorotate was not obtained. Formation of the hydantoin proceeds with loss of optical activity.

Treatment of **4** with a second equivalent of methoxide and subsequent reaction with benzyl bromide did not give incorporation of a second benzyl group, most likely due to incomplete deprotonation of the second amide hydrogen. However, when **4** was reacted with benzyl bromide and potassium carbonate in DMF at 50  $^\circ\text{C}$ , a pale oil was obtained after purification on silica gel. The NMR spec-

(1) (a) Keys, L. D., III; Johnston, M. *J. Am. Chem. Soc.* 1985, 107, 486. (b) Hines, V.; Keys, L. D., III; Johnston, M. *J. Biol. Chem.* 1986, 261, 11386.

(2) Hannon, S. J.; Kundu, N. G.; Hertzberg, R. P.; Bhatt, R. S.; Heidelberger, C. *Tetrahedron Lett.* 1980, 21, 1105.

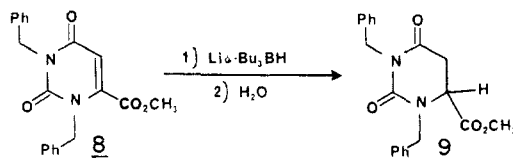
(3) Batt, R. D.; Martin, J. K.; Ploeser, J. M.; Murray, J. *J. Am. Chem. Soc.* 1954, 76, 3663.

<sup>†</sup> University of Chicago.

<sup>‡</sup> Present address: Hoffmann LaRoche, Nutley, NJ 07110.

<sup>§</sup> University of Indiana.

trum of this material indicated the formation of the 1,3-dibenzyl hydantoin **5**. There was no evidence for *N*<sup>1</sup>,*N*<sup>3</sup>-dibenzyl dihydroorotate **2** having formed. Alternately, when we applied the reduction method of Heidelberg to methyl 1,3-dibenzyl orotate (**8**),<sup>2</sup> methyl 1,3-dibenzyl dihydroorotate (**9**) was afforded cleanly. The <sup>1</sup>H NMR spectrum of **9** is unambiguously distinct from that given by **5**.



Reaction of **5** with *n*-butyllithium and iodomethane led to a single product that gave an <sup>1</sup>H NMR spectrum consistent with the 5-methylhydantoin **6**; the diagnostic resonances included a methyl singlet ( $\delta$  1.28) and a pair of single-proton doublets ( $\delta$  2.48, 2.85), each with a *J* value (17.1 Hz) indicative of geminal hydrogen coupling.

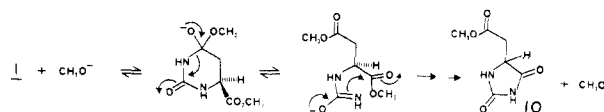
It occurred to us that compounds **4**, **5**, and **6** might arise subsequent to an initial methoxide-catalyzed rearrangement of **1** to its thermodynamically more stable isomer methyl hydantoin-5-acetate (**10**). It was clear that unambiguous structural determination of at least one of the compounds of Scheme II was required, and an X-ray crystallographic analysis was indicated. Since **5** and **6** were not crystalline, attention was turned to compound **4**.

When **4** is refluxed in neat acetic anhydride,<sup>4</sup> the *N*<sup>1</sup>-acetylhydantoin **7** is obtained in excellent yield.<sup>5</sup> This compound was easily crystallized from ethyl acetate, giving crystals amenable to X-ray analysis. The crystals of **7** are orthorhombic; they occupy the space group *Pbca*, which demonstrates that the crystal contains the 5*R* and 5*S* enantiomers of **7**. A perspective drawing of the 5*S* isomer is available as supplementary material.

The X-ray result confirmed that, under the basic conditions designed for *N*-alkylation of **1**, rearrangement of the heterocycle occurs to generate a hydantoin ring. Presumably, *N*-benzylation to give **4** occurred after rearrangement. In support of this conclusion, the rearrangement of **1**  $\rightarrow$  **10** proceeds readily in refluxing methanol in the absence of benzyl bromide. A reasonable mechanism for this rearrangement involves methoxide addition to the C4-carbonyl of **1**, with subsequent expulsion of the amido group to open the dihydropyrimidine ring (Scheme III). After rotation into proximity with the other carbomethoxy group, the amido function adds to the ester—generating the new five-membered hydantoin ring system. Expulsion of methoxide completes the rearrangement.

The sequence of Scheme III is, to our knowledge, the first example of base-catalyzed conversion of a dihydroorotate ester to a hydantoin-5-acetate ester. Rearrangement of the dihydroorotic acid ring is known to occur under acid-catalyzed conditions.<sup>6</sup> However, dihydroorotic acid may be refluxed in a 2-fold excess of methoxide in methanol for extended periods without rearrangement to the corresponding hydantoin.<sup>1,6,7</sup> In this latter case, one expects that an ionized C6-carboxylate precludes the intramolecular amido group addition required to form a five-membered ring.

Scheme III



Inasmuch as compounds **4**, **5**, **6**, **7**, and **10** are all obtained as optically inactive materials, it is clear that rearrangement of the dihydroorotate heterocycle is accompanied by racemization. While we have not investigated this phenomenon in detail, it seems reasonable that methoxide would also catalyze epimerization at C5 of a product hydantoin following ring contraction. Racemization of **1** prior to rearrangement seems less likely. When dihydroorotic acid is refluxed in ethanol-*d* with sodium ethoxide, solvent deuterons become incorporated into the C5-methylene position, but exchange of the C6-methine hydrogen does not occur.<sup>1a</sup> The corresponding methine proton of the hydantoin nucleus is obviously acidic, as evidenced by the regioselective C5-alkylation in the conversion **5**  $\rightarrow$  **6**. Epimerization of a ring-opened intermediate cannot, of course, be ruled out.

Clearly the rearrangement described is to be avoided in pursuit of 5-alkyl derivatives of dihydroorotate.<sup>8</sup> On the other hand, Buntain and co-workers<sup>9</sup> have recently reported on several hydantoin-5-acetate esters, to be added to the synthetic repertoire available for these structures.

### Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. <sup>1</sup>H NMR spectra were recorded at 270 MHz on a Bruker HX 270 instrument (modified with the Nicolet 1180 computer) using tetramethylsilane as an internal reference. Chemical shift values are in ppm. Mass spectra were obtained through electron impact ionization on a VG Analytical 70-250HF mass spectrometer. Infrared data were obtained on a Perkin-Elmer Model 241 spectrophotometer, and optical rotations were measured on a Perkin-Elmer Model 283 polarimeter. Analytical data (C, H, N) were obtained by MicAnal Organic Microanalysis Co., Tucson, AZ.

Analytical thin layer chromatography (TLC) was performed on plates (40  $\times$  80 mm) of Polygram Sil G/UV<sub>254</sub> (Machery-Nagel). Preparative TLC was performed on 2000- $\mu$ m silica gel GF/F plates (10  $\times$  10 cm, Analtech). Preparative column chromatography utilized Merck Grade 60 silica gel (230–400  $\mu$ m). Methyl 1,3-dibenzyl orotate (**8**) was prepared from methyl orotate (Sigma Chemical Co.) using standard methods.<sup>2</sup> Lithium (tri-*sec*-butyl)borohydride was obtained as a 1.0 M solution in THF, and *n*-butyllithium was 1.5 M in hexanes; both reagents were obtained from Aldrich. Methanol was dried by distillation from I<sub>2</sub>-activated Mg, and THF was distilled from sodium/benzophenone under N<sub>2</sub>.

**Methyl 3-Benzylhydantoin-5-acetate (4).** A dry flask equipped with a reflux condenser was charged with methyl (*S*)-dihydroorotate (1.20 g, 7.00 mmol) and dry methanol (50 mL) was distilled into this flask under a dry N<sub>2</sub> atmosphere. Sodium metal (177 mg, 7.70 mmol) was added to the well-stirred suspension and, after dissolution of the metal, benzyl bromide (1.44 g, 8.41 mmol) was added. The solution was refluxed for 3 h and was cooled to ambient temperature before being poured into saturated NH<sub>4</sub>Cl (75 mL). The mixture was extracted with ethyl

(4) Spector, L. B.; Keller, E. B. *J. Biol. Chem.* **1958**, *232*, 185.

(5) The deacetyl hydantoin **4** is regenerated quantitatively by stirring **7** in methanol at ambient temperature.

(6) Miller, C. S.; Gordon, J. T.; Engelhardt, E. L. *J. Am. Chem. Soc.* **1953**, *75*, 6086.

(7) Blattman, P.; Retey, J. *Eur. J. Biochem.* **1972**, *30*, 130.

(8) In fact, we have recently developed methods for obtaining compounds such as **3** (by the sequence proposed in Scheme I) that avoid rearrangement of the dihydroorotate nucleus. We shall provide these results in a separate communication.

(9) Buntain, I. G.; Suckling, C. J.; Wood, H. C. S. *J. Chem. Soc., Chem. Commun.* **1985**, 242.

acetate (3 × 75 mL), and the combined organic extracts were washed with water (75 mL) and dried over MgSO<sub>4</sub>. The solvent was removed, and the resulting residue was purified on a silica gel column (3.8 × 40 cm) by applying the sample and then washing the column with 700 mL of ethyl acetate/petroleum ether. The product was eluted with ethyl acetate, and the appropriate fractions were combined, evaporated, and dried in vacuo: yield, 0.815 g (44%) of a white crystalline solid; mp 106.5–107.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33 (m, 10 H, Ar), 4.64 (s, 2 H, benzylic), 4.33 (m, 1 H, H6), 3.69 (s, 3 H, methyl ester), 3.03 (dd, *J* = 17.4 and 3.11 Hz, 1 H, H5), 2.58 (dd, *J* = 17.4 and 10.2 Hz, 1 H, H5); IR (KBr) 3250 (br), 1732 (shoulder), 1704 cm<sup>-1</sup>; MS, *m/z* (relative intensity) 262 (100), 231 (13), 202 (13), 161 (20), 160 (26), 132 (33), 106 (32), 102 (29), 91 (74), 70 (18).

**Methyl 1,3-Dibenzylhydantoin-5-acetate (5).** Method A. Compound 4 (263 mg, 1.00 mmol) and anhydrous K<sub>2</sub>CO<sub>3</sub> (173 mg, 1.25 mmol) were slurried in dry DMF (3 mL) under a N<sub>2</sub> atmosphere and benzyl bromide (188 mg, 1.10 mmol) was added. The mixture was maintained at 50 °C for 35 h and was cooled to ambient temperature and poured into saturated NH<sub>4</sub>Cl (15 mL). The mixture was extracted with ethyl acetate (3 × 15 mL), and the combined organic extracts were washed with water (2 × 15 mL) and dried over MgSO<sub>4</sub>. The solids were removed, and the filtrate was evaporated to a small volume and subjected to preparative TLC (ethyl acetate/petroleum ether, 1:2); the compound (*R<sub>f</sub>* 0.41) was eluted with ethyl acetate. After filtration, the solvent was stripped, and the residue was dried in vacuo: yield, 201.3 mg (57%) of a colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33 (m, 10 H, Ar), 4.77 (d, *J* = 15.4 Hz, 1 H, benzylic), 4.72 (distorted d, 2 H, benzylic), 4.32 (d, *J* = 15.4 Hz, 1 H, benzylic), 4.06 (apparent t, *J* = 4.70 Hz, 1 H, H6), 3.40 (s, 3 H, methyl ester), 2.76 (apparent dd, *J* = 4.7 and 1.1 Hz, 2 H, H5); IR (KBr) 1770 (w), 1736 (shoulder), 1710 cm<sup>-1</sup>; MS, *m/z* (relative intensity) 352 (46), 292 (6), 261 (30), 132 (16), 106 (10), 91 (100).

**Method B.**<sup>10</sup> Compound 4 (262 mg, 1.00 mmol) in dry THF (5 mL) was cooled to -78 °C, and *n*-butyllithium (1.05 mmol, 1.55 M in hexane) was added. After 10 min, benzyl bromide (188 mg, 1.10 mmol) was added, the cooling bath was removed, and the solution was warmed to ambient temperature over 20 min; the solution was then refluxed for 2.5 h. After being cooled to room temperature, the solution was poured into saturated NH<sub>4</sub>Cl (20 mL), was extracted with ethyl acetate (4 × 20 mL), and was dried over MgSO<sub>4</sub>. Removal of solvent afforded a residue which was purified by preparative TLC (ethyl acetate/petroleum ether, 2:1); the product (*R<sub>f</sub>* 0.55) was eluted with ethyl acetate/acetone. After filtration, the solvent was removed, and the residue was dried in vacuo at 60–70 °C, affording 243 mg (69%) of a pale oil. Analytical data were identical with those reported above for 5 prepared by method A.

**Methyl 1,3-Dibenzyl-5-methylhydantoin-5-acetate (6).** Compound 5 (138 mg, 0.39 mmol) was dissolved in dry THF (3 mL), and the solution was cooled to -78 °C. A hexane solution of *n*-butyllithium (0.41 mmol, 1.55 M) was added dropwise, and the solution was stirred for 10 min before methyl iodide (84 mg, 0.59 mmol) was added. The cooling bath was removed, and the solution was brought to room temperature over the next 15 min; it was then poured into saturated NH<sub>4</sub>Cl (15 mL) and was extracted with ethyl acetate (3 × 15 mL). The organic extract was washed with water (2 × 15 mL) and dried over MgSO<sub>4</sub>. The solvent was removed, and the residue was purified by preparative TLC (ethyl acetate/petroleum ether, 1:3). The compound (*R<sub>f</sub>* 0.29) was eluted with ethyl acetate, and the filtered eluate was evaporated and dried in vacuo: yield, 78.5 mg (55%) of a yellowish oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35 (m, 10 H, Ar), 4.75 (s, 2 H, benzylic), 4.68 (d, *J* = 15.7 Hz, 1 H, benzylic), 4.36 (d, *J* = 15.7 Hz, 1 H, benzylic), 3.21 (s, 3 H, methyl ester), 2.85 (d, *J* = 17.1 Hz, 1 H, H5), 2.48 (d, *J* = 17.1 Hz, 1 H, H5), 1.28 (s, 3 H, 6-methyl); IR (KBr) br 1774, 1743 (shoulder) 1713; MS, *m/z* (relative intensity) 366 (35), 293 (15), 275 (10), 132 (16), 106 (13), 91 (100).

**Methyl 1-Acetyl-3-benzylhydantoin-5-acetate (7).** Compound 4 (150 mg, 0.57 mmol) in 1.5 mL of acetic anhydride was refluxed for 6 h and then cooled to ambient temperature. The solvent was removed in vacuo overnight. The residue was purified

by preparative TLC (ethyl acetate/petroleum ether, 1:2), and the product (*R<sub>f</sub>* 0.45) was eluted with ethyl acetate/acetone. The filtered eluate was stripped of solvent, and the sample was dried in vacuo at 60 °C: yield, 164 mg (94%) of a white crystalline solid; mp 89.5–91.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.39 (m, 5 H, Ar), 4.73 (s, 2 H, benzylic), 4.61 (m, 1 H, H6), 3.53 (s, 3 H, methyl ester), 3.40 (dd, *J* = 17.6 and 4.75 Hz, 1 H, H5), 3.08 (dd, *J* = 17.6 and 3.28 Hz, 1 H, H5), 2.56 (s, 3 H, acetyl); IR (KBr) 1784 (w), 1725, 1710, 1704 cm<sup>-1</sup>; MS, *m/z* (relative intensity) 304 (66), 262 (81), 202 (43), 132 (39), 106 (35), 91 (100).

**Methyl 1,3-Dibenzyl-dihydroorotate (9).** Methyl 1,3-dibenzylorotate (8) (1.04 g, 2.98 mmol) dissolved in 15 mL of dry THF was cooled to -78 °C. L-Selectride (3.28 mmol) was added dropwise, as a solution in THF, and the resulting solution was stirred for 10 min. Water (81 mg, 4.5 mmol) was added and the solution was brought to ambient temperature over the next 10 min. The reaction mixture was poured into saturated NH<sub>4</sub>Cl (40 mL) and was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with water (2 × 40 mL) and dried over MgSO<sub>4</sub>. After removal of solvent, the residue was purified by TLC (ethyl acetate/petroleum ether). The compound (*R<sub>f</sub>* 0.53) was eluted with ethyl acetate, and the filtered eluate was stripped of solvent and dried in vacuo: yield, 541 mg (51%) of a pale oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.32 (m, 10 H, Ar), 5.28 (d, *J* = 15.0 Hz, 1 H, benzylic), 5.02 (s, 2 H, benzylic), 4.11 (d, *J* = 15.0 Hz, 1 H, benzylic), 3.93 (dd, *J* = 7.14 and 2.00 Hz, 1 H, H6), 3.55 (s, 3 H, methyl ester), 2.97 (dd, *J* = 16.86 and 2.00 Hz, 1 H, H5), 2.84 (dd, *J* = 16.86 and 7.15 Hz, 1 H, H5); IR (KBr) 1741, 1717, 1670 cm<sup>-1</sup>; MS, *m/z* (relative intensity) 352 (54), 293 (62), 181 (14), 132 (12), 106 (19), 91 (100).

**Methyl Hydantoin-5-acetate (10).** Compound 1 (172 mg, 1.00 mmol) in dry methanol (15 mL) was treated with sodium metal (25 mg, 1.1 mmol) under an N<sub>2</sub> atmosphere. The solution was refluxed for 3 h and then cooled to ambient temperature. Glacial acetic acid (180 mg, 3.00 mmol) was added and the solvent was stripped under vacuum. The mixture was slurried in ethyl acetate (100 mL) and the solids were filtered. The filtrate was reduced to approximately 3 mL and was applied to a silica gel column (2 × 11 cm) previously equilibrated with ethyl acetate. The product was eluted with this solvent and then was evaporated under reduced pressure and crystallized overnight at -15 °C: yield, 94 mg (55%) of white crystals; mp 121–122.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.52 (br s, 1 H, H3), 6.30 (br s, 1 H, H1), 4.41 (m, 1 H, H5), 3.76 (s, 3 H, methyl ester), 3.04 (dd, *J* = 17.5 and 3.07 Hz, 1 H, CH-CO<sub>2</sub>), 2.67 (dd, *J* = 17.5 and 10.1 Hz, 1 H, CH-CO<sub>2</sub>); IR (KBr) 3200 (br), 1770, 1711 cm<sup>-1</sup>; MS, *m/z* (relative intensity) 172 (18), 140 (28), 112 (100), 99 (40), 74 (60), 69 (15).

**Registry No.** 1, 39681-15-7; 4, 104834-76-6; 5, 104834-77-7; 6, 104834-78-8; 7, 104848-68-2; 8, 104834-80-2; 9, 104834-80-2; 10, 63760-88-3; benzyl bromide, 100-39-0; methyl iodide, 74-88-4.

**Supplementary Material Available:** Fractional coordinates and isotropic thermal parameters for methyl 1-acetyl-3-benzylhydantoin-5-acetate (7), together with an ORTEP drawing of the compound (3 pages). Ordering information is given on any current masthead page.

### Preparation of Ceph-3-em Esters Unaccompanied by Δ<sup>3</sup> → Δ<sup>2</sup> Isomerization of the Cephalosporin

Shahriar Mobashery and Michael Johnston\*

Departments of Chemistry and of Biochemistry and Molecular Biology, Searle Chemistry Laboratory, The University of Chicago, Chicago, Illinois 60637

Received April 1, 1986

Synthetic manipulation of the cephem nucleus routinely requires the preparation of cephalosporin C-9 esters, a number of which—those that bear a physiologically labile group—are actually employed as pro-drugs for oral administration of β-lactams.<sup>1</sup> These esters are commonly

(10) This is the preferred method for preparation of 5.