NMR 0.8–1.1 (CH_3, t, 6 H), 3.1–4.0 (NCH, NCH_2, m, 6 H), 1.2–2.2 (CH_2CH_2, m, 16 H), 3.7 (OCH_3, s, 3 H), 3.8–4.6 (OCH_2, m, 4 H); EIHRMS, m/z 418.223 92 ($C_{19}H_{35}N_2O_6P$ requires 418.223 23). Anal. Calcd for $C_{19}H_{35}N_2O_6P$: C, 54.55; H, 8.37; N, 6.70. Found: C, 54.50; H, 8.41; N, 6.63.

Preparation of *N*-[*N'*-[Bis(butyloxy)phosphinyl]prolyl]proline 7. Preparation of 7a as the General Procedure. Lithium hydroxide monohydrate (0.30 g, 2.4 mmol, 3.0 equiv) was added to a solution of **6a** (1.0 g, 2.4 mmol) in 3 mL of THF/MeOH/H_2O (3:1:1) at 20 °C, the resulting reaction mixture was stirred at 60 °C for 5 h, then water (3 mL) was added, and the organic solvent was removed with a rotary evaporator. The aqueous phase was washed with EtOAc (2 × 3 mL), then acidified to pH 3 with 10% aqueous HCl (3 mL) under ice-cold-bath conditions, and extracted with EtOAc (5 × 15 mL). The combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel using ethanol/petroleum ether/HOAc (15:50:1) as eluent afforded **7a** (0.74 g, 76.3%) as a colorless oil. **7a**: ^1H NMR 0.6–1.0 (CH_3, t, 6 H), 1.1–2.2 (CH_2CH_2, m, 16 H), 2.9–3.4 (NCH, NCH_2, m, 6 H), 3.8–4.5 (OCH_2, m, 4 H), 10.7 (CO_2H, s, 1 H). **7b**: ^1H NMR 1.1–1.4 (CH_3, d, 6 H), 1.9–2.3 (CH_2CH_2, m, 8 H), 3.0–3.4 (NCH, NCH_2, m, 6 H), 3.8–4.4 (OCH_2, m, 4 H), 9.5 (CO_2H, s, 1 H). **7a**: EIHRMS, m/z 404.207 ($C_{18}H_{33}N_2O_6P$ requires 404.208), 262.156 68 ($C_{12}H_{25}NO_3P$ requires 262.157 18), 206.0946 ($C_6H_{17}NO_3P$ requires 206.094 58), 150.031 78 ($C_4H_9NO_3P$ requires 150.031 98).

Preparation of *N*-Prolylproline Hydrochloride (11). A solution of 1.0 g (2.48 mmol) of **7a** in 30 mL of dry Et_2O was saturated with dried HCl(g) below 0 °C. After being kept overnight at 0 °C, the precipitate was filtered and washed with petroleum ether. The crude product was recrystallized from ethanol/ethyl ether (1:2), giving colorless needles: mp 89–91 °C[9] (0.44 g, 71%); ^1H NMR (D_2O) 0.8–1.3 (CH_2CH_2, m, 8 H), 2.2–4.1 (NCH, NCH_2, m, 6 H); IR $\nu_{C(O)OH}$ 1735, $\nu_{C(O)N}$ 1665 cm^{-1}.

Thermolysis of *N*-[*N'*-(Dialkoxyphosphinyl)prolyl]proline 7. A solution of **7a** (1.69 g, 4.18 mmol), in 10 mL of 1-butanol was stirred at 105–110 °C for 6 h. After removal of the solvent by distillation in vacuo, an oily residue was obtained. Column chromatography on silica gel using ethanol/petroleum ether/HOAc (15:50:1) as gradient eluent afforded **10a** (0.22 g, 25%) as a colorless oil, compound **8** (0.34 g, 42%) as a crystalline solid, which was recrystallized from CH_2Cl_2/petroleum ether (1:3), giving colorless crystals, mp 142–143 °C,[10] and **9** (0.55 g, 28.6%) as a colorless oil. ^1H NMR 0.8–1.3 (CH_3, t, 6 H), 1.4–1.6 (CH_2CH_2, m, 8 H), 2.0 (OH, s, 1 H), 3.9–4.1 (OCH_2, m, 4 H). **8**: ^1H NMR 1.9–2.3 (CH_2CH_2, m, 8 H), 3.4–3.6 (NCH, NCH_2, m, 6 H); EIHRMS, m/z 194.104 88 ($C_{10}H_{14}N_2O_2$ requires 194.105 50). **9**: ^1H NMR 0.7–1.0 (CH_3, t, 9 H), 1.1–2.1 (CH_2CH_2, m, 20 H), 3.0–3.4 (NCH, NCH_2, m, 6 H), 3.8–4.3 (OCH_2, m, 6 H); FABHRMS, m/z 460.2706 ($C_{22}H_{42}N_2O_6P$ requires 460.2703). The thermolysis of **7b** was carried out in a similar manner as described above, using toluene as solvent instead of 1-butanol. Isolation by preparative TLC using EtOH/petroleum ether/HOAc (15:50:1) as eluent afforded **10b** (0.25 g, 48.7%): ^1H NMR 0.8–1.4 (CH_3, d, 12 H), 3.8–4.2 (CH, m, 2 H), 2.5 (OH, s, 1 H). There was no analogue of **9** formed.

Ester Exchange Reaction of *N*-[*N'*-[Bis(butyloxy)phosphinyl]prolyl]proline (7a). A solution of **7a** (0.5 g, 1.23 mmol) in 10 mL of ethanol was stood at room temperature (20 °C) for about 10 days. Several products were formed as checked by TLC. After removal of the solvent, a light yellowish oil was obtained. **12**: EIHRMS, m/z 404.207 ($C_{18}H_{33}N_2O_6P$ requires 404.208). **13**: EIHRMS, m/z 432.238 ($C_{20}H_{37}N_2O_6P$ requires 432.239).

Acknowledgment. We thank the National Science Foundation for funding (Chemistry) 2860227 (Y.-f.Z.).

Registry No. **2**, 147-85-3; **3a**, 121252-81-1; **5**, 2133-40-6; **6a**, 121252-82-2; **7a**, 121252-83-3; **7b**, 121252-87-7; **8**, 19943-27-2; **9a**, 121252-84-4; **10a**, 107-66-4; **10b**, 1611-31-0; **11**, 76932-06-4; **12**, 121252-85-5; **13**, 121252-86-6; $(BuO)_2P(O)H$, 1809-19-4.

(9) Davis, N. C.; Smith, E. L. *J. Biol. Chem.* **1953**, *200*, 373.
(10) Rothe, M.; Mazdnek, J. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*(4), 293.

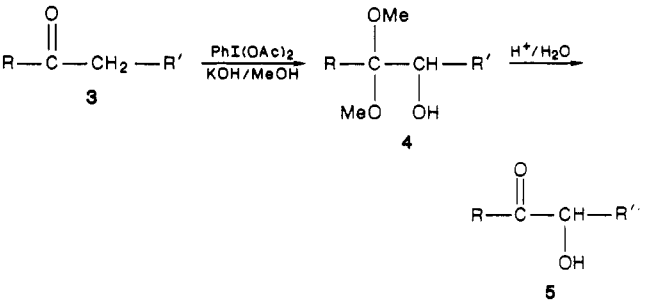
Synthesis and Structure of 2α-Hydroxytropan-3-one

Robert M. Moriarty,* Om Prakash,† Pushpa R. Vavilikolanu, Radhe K. Vaid, and Wade A. Freeman

Department of Chemistry, University of Illinois at Chicago, Box 4348, Chicago, Illinois 60680

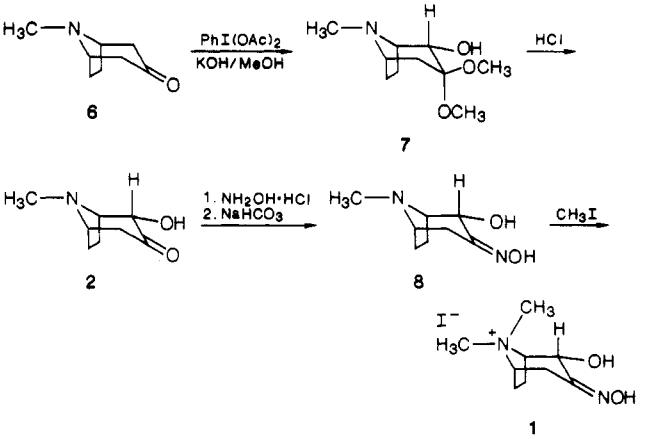
Received December 20, 1988

As part of our program directed toward the synthesis of azabicyclo keto oximes as potentially useful acetylcholinesterase reactivators, we synthesized 2α-hydroxytropan-3-one oxime methiodide (**1**). A key intermediate in this synthesis is 2α-hydroxytropan-3-one (**2**), a compound already reported in the literature.[1] Based on our recent work on hypervalent iodine oxidation, it appeared attractive to use this reaction, which entails conversion of enolizable ketones to α-hydroxy dimethyl acetals (**4**) followed by acid hydrolysis (**3** → **4** → **5**).[2]



We have already shown that one of the major advantages of this method is the successful α-hydroxylation of ketones containing an amino functionality, i.e. the nitrogen of the amino group (primary, secondary, or tertiary) is not oxidized under the reaction conditions.[3a,b]

Tropan-3-one (**6**), upon oxidation with iodobenzene diacetate in methanolic potassium hydroxide, afforded 2α-hydroxytropan-3-one dimethyl acetal (**7**), isolated by column chromatography, in 30–35% yield. Hydrolysis of **7**, using 3 N HCl, gave **2**, mp 65–66 °C in 60% yield. Oximation of **2**, followed by quaternization with methyl iodide, resulted in **1**, obtained as a colorless crystalline solid.



The structures of all the products were confirmed by their spectral data and elemental analyses. A determination of the X-ray structure of **1** was undertaken for two reasons. The first was an absolute structural proof, and

† On study leave from Kurukshetra University, Kurukshetra, India.

0022-3263/89/1954-4008$01.50/0

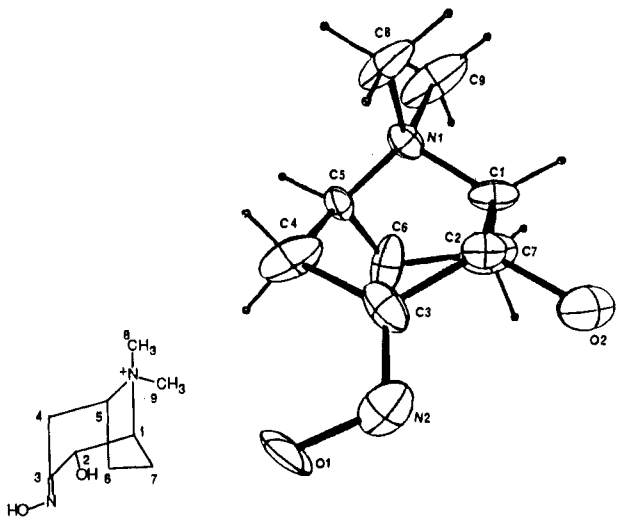
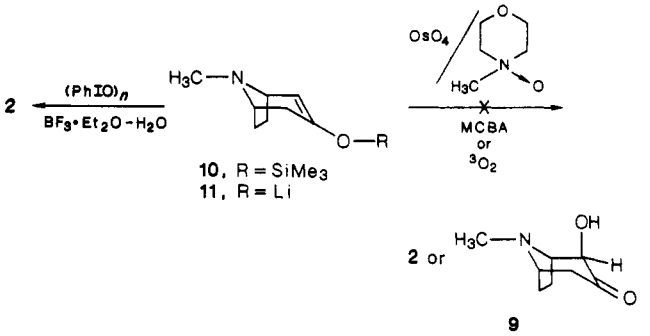


Figure 1. X-ray crystallograph of 2α-hydroxytropan-3-one oxime methiodide (1).

secondly, to obtain molecular parameters for development of structure versus activity relationship in acetylcholinesterase studies.[4] The X-ray structure of 1 is presented in Figure 1.

It may be noted that 2α-hydroxytropan-3-one (2) was previously described by Sarel and Dykman in 1976, but the melting point they reported (101–103 °C) is different from ours (65–66 °C).[5] Since the X-ray structure of our oxime methiodide showed the hydroxyl to be α (equatorial), two possible explanations for the difference existed; either the hydroxyl had undergone epimerization during conversion to the oxime or Sarel and Dykman had made the wrong assignment. Attempts to synthesize 2β-hydroxytropan-3-one (9) by possible acid-catalyzed isomerization of either 7 or 2 showed no change in configuration. Other reported methods for inversion ($C_2H_5CO_2Cs^+$/DMF:[6a] $EtO_2CN{=}NCO_2Et/Ph_3P/PhCO_2H$[6b]) also failed to give 9. Alternatively, we attempted the synthesis of 9 by other α-hydroxylation procedures known in the literature. Tropan-3-one enol silyl ether (10) was prepared using the method described by House et al.[7] and treatment with OsO_4/N-methylmorpholine oxide[8] or m-chloroperbenzoic acid[9] or addition of $^3O_2$ to enolate (11)[10] did not yield the α-hydroxylated product. Our recently reported alternative approach,[11] which involves the oxidation of the enol silyl ether using iodosobenzene and $BF_3{\cdot}Et_2O$ and water, also gave 2 from 10. Failure to isolate any α-hydroxylation product, either α or β, from any of the other approaches,[8-10] quite apart from the stereochemical question, indicates the usefulness of the hypervalent iodine methods.



The control experiments allow us to conclude that the conditions used in oximation do not cause epimerization of the hydroxyl; it is α (equatorial) contrary to Sarel and Dykman.[5]

Experimental Section

Melting points are uncorrected. The IR spectra were obtained using a Unicalm SP1000 spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were recorded on a Varian spectrometer using TMS as an internal standard. Signals for hydroxyl group protons were detected by addition of D_2O. Chemical shifts for different protons were determined by performing decoupling experiments on 2. Mass spectra were measured with Hewlett-Packard GC/MS 5985 apparatus.

Tropan-3-one and iodobenzene diacetate are commercial products (Aldrich).

2α-Hydroxytropan-3-one Dimethyl Acetal (7). Tropan-3-one (6) (0.1 mol, 13.9 g) was dissolved in 100 mL of absolute methanol and added dropwise to a stirred solution of potassium hydroxide (0.3 mol, 16.80 g) in methanol (250 mL) over a period of 20 min at 0–5 °C. After the solution was stirred for an additional 10 min, iodobenzene diacetate (0.11 mol, 36.5 g) was added in 5–6 portions during 10 min, and the reaction mixture was allowed to stir overnight at room temperature. Most of the methanol was evaporated in vacuo, and to the residue was added 250 mL of water. The resulting mixture was saturated with solid ammonium chloride and extracted with $CHCl_3$ (6 × 150 mL). The combined extracts were dried and concentrated in vacuo to yield the crude product. Column chromatography on silica gel using ethyl acetate and methanol (70:30) as eluant gave 6.63 g (33%) of colorless crystalline product (from hexane) mp 85–86 °C. Initial elution yielded iodobenzene and the balance of material as more highly methoxylated ketones, which were not characterized. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.70; H, 9.45; N, 6.96. Found: C, 59.53; H, 9.49; N, 6.70. IR ($CHCl_3$): 3550 cm^{-1} (O–H, str). ^1H NMR ($CDCl_3$) δ: 2.31 (s, 3 H, NCH_3), 3.05 (m, 2 H, C_1-H, C_5-H), 3.30 (s, 3 H, C_3-OCH_3), 3.89 (b, 1 H, C_1-OH). ^{13}C NMR ($CDCl_3$) δ: 97.83 (C_3), 73.90 (C_2), 66.13 (C_1), 59.99 (5), 50.40 (OCH_3), 47.85 (OCH_3), 39.65 (C_8), 36.31 (C_4), 24.29 (C_6), 20.21 (C_7); MS m/z,

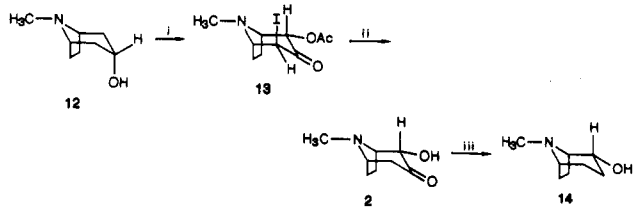
(1) Sarel, S.; Dykman, E. *Tetrahedron Lett.* **1976**, 3725; *Heterocycles* **1981**, *15*, 719.

(2) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244. Moriarty, R. M.; Hou, K. C.; Prakash, I.; Arora, S. K. *Org. Synth.* **1986**, *64*, 138. In the seconed paper, the use of o-iodosobenzoic acid is presented.

(3) (a) Moriarty, R. M.; Prakash, O.; Karalis, P.; Prakash, I. *Tetrahedron Lett.* **1984**, *25*, 4745. (b) Moriarty, R. M.; Prakash, O.; Thachet, C. T.; Musallam, H. A. *Heterocycles* **1985**, *23*, 633.

(4) The details of this study will be published elsewhere.

(5) These authors[1] obtain the compound identified as 2 from the following sequence of reactions:



i = $Pb(OAc)_4$-I_2, C_6H_6; ii = Raney Ni[H]; iii = (1) NH_2NH_2, KOH; (2) Wolff-Kishner.

2α-Hydroxytropane (14) was identified by positive comparison with an authentic sample of the hydrochloride and picrate. In the above scheme, it is possible that epimerization might occur under the conditions of the Wolff-Kishner reduction (2 → 14). Thus, a putative 2β-hydroxytropan-3-one might yield 14.

(6) (a) Kruizinga, W. H.; Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321. (b) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427.

(7) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

(8) McCormick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607.

(9) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427.

(10) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. *J. Chem. Soc.* **1962**, 1578.

(11) Moriarty, R. M.; Prakash, O.; Duncan, M. P. *Synthesis* **1985**, *943*; *J. Chem. Soc., Perkin Trans. 1* **1987**, 1781.

(percent abundance): 201 (M, 58), 170 (84), 97 (63), 96 (68), 82 (100).

2α-Hydroxytropan-3-one (2). To a solution of **7** (0.025 mol, 5.05 g) in water (50 mL) was added 50 mL of 6 N HCl, and the resulting solution was kept at room temperature for 1 h. The reaction mixture was made basic with $NaHCO_3$ and then saturated with solid NH_4Cl. Extraction with $CHCl_3$ (6 × 100 mL) followed by drying over $MgSO_4$ and concentration in vacuo gave crude product as an oil, which was crystallized from hexane and yielded 2.33 g (60%) of colorless crystalline solid, mp 65–66 °C. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.93; H, 8.39; N, 9.03. Found: C, 61.75; H, 8.43; N, 8.95. IR ($CHCl_3$, cm^{-1}): 1715 (C=O str), 3510 (O—H, str); ^1H NMR ($CDCl_3$) δ: 2.52 (s, 3 H, NCH_3), 3.48 (m, 2 H, C_1-H, C_5-H), 3.74 (b, 1 H, O*H*), 4.31 (d, 1 H, C_2-*H*); ^{13}C NMR ($CDCl_3$) δ: 188.14 (*C*=O), 76.45 (C_2), 67.04(C_1), 62.30 (C_5), 46.15 (C_4), 38.86 (C_8), 26.65 (C_6), 21.81 (C_7); MS (20 eV) *m/z* (percent abundance): 155 (M, 47), 125 (2), 124 (2), 112 (16), 98 (30), 96 (40), 82 (100).

2α-Hydroxytropan-3-one Oxime Hydrochloride (8a). To a solution of hydroxylamine hydrochloride (0.011 mol, 0.76 g) in methanol (20 mL) was added a solution of **2** (0.010 mol, 1.55 g) in methanol (10 mL) with stirring. An exothermic reaction occurred, and a colorless solid separated from solution. The mixture was cooled, and the resulting solid was collected by filtration in 90% yield (1.85 g), mp 195–98 °C dec. ^1H NMR (DMSO) δ: 1.39–2.32 (m, 4 H, protons at C_6 and C_7 carbon atoms), 2.55 (dd, 1 H, C_4-*H*), 3.14 (dd, 1 H, C_4-*H*), 2.72 (s, 3 H, N-CH_3), 3.89 (m, 2 H, C_1-, C_5-*H*), 4.87 (d, 1 H, C_2-*H*), 5.64 (b, 1 H, C_2-O*H*), 11.81 (b, 1 H, =NO*H*), 11.17 (s, 1 H, hydrochloride proton).

2α-Hydroxytropan-3-one Oxime (8). Oxime hydrochloride **8a** (1.85 g) was dissolved in water (20 mL) and basified by addition of excess of solid sodium bicarbonate. The resulting solution was saturated with solid ammonium chloride, and oxime **8** was isolated by extraction with chloroform (8 × 25 mL), mp 166–169 °C (EtOH); yield 72% (1.00 g). Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.47; H, 8.24; N, 16.47. Found: C, 56.30; H, 8.31; N, 16.28. ^1H NMR ($CDCl_3$) δ: 1.25–2.32 (m, 4 H, protons at C_6 and C_7 carbon atoms), 2.35 (s, 3 H, NCH_3), 2.04 (dd, 1 H, C_4-*H*), 2.98 (dd, 1 H, C_4-*H*), 3.21 (m, 2 H, C_1-*H*, C_5-*H*), 4.02 (b, 1 H, C_2-O*H*), 4.31 (d, 1 H, C_2-*H*).

2α-Hydroxytropan-3-one Oxime Methiodide (1). To a solution of the above oxime (**8**) (1 g) in dry ethanol was added methyl iodide (3 mL), and the solution was left overnight at room temperature. Pure colorless crystalline methiodide (92%), mp 189–92 °C dec, was collected by filtration. Anal. Calcd for $C_9H_{17}IN_2O_2$: C, 34.61; H, 5.45; N, 8.97; I, 40.70. Found: C, 34.42; H, 5.49; N, 8.91; I, 40.52. ^1H NMR (DMSO) δ: 3.15 (s, 3 H, N^+CH_3), 3.32 (s, 3 H, N^+CH_3), 3.90 (m, 1 H, C_1-*H*), 4.05 (m, 1 H, C_5-*H*), 4.76 (t, 1 H, C_2-*H*) (collapses to doublet on decoupling OH group proton), 5.83 (d, 1 H, C_2-O*H*).

Tropan-3-one Silyl Enol Ether (10). Compound **10** was prepared from tropan-3-one (**6**) according to the general method A of House et al.[7] However, dilute hydrochloric acid was not used in the workup because acid hydrolysis of silyl enol ether occurred to a significant extent. Purification of crude product by distillation gave **10** in 77% yield, bp 97–99 °C/25 mm. IR (neat, cm^{-1}): 1685 (C=C, str in silyl enol ether). MS: *m/z* 207 (M^+).

Oxidation of 10 Using Iodosobenzene, Boron Trifluoride Etherate, and Water. Silyl enol ether **10** (0.01 mol, 2.07 g) was added to a suspension of iodosobenzene (0.011 mol, 2.42 g) and boron trifluoride etherate (0.02 mol, 2.48 g) in water (50 mL) at 0 °C. The mixture was stirred for 4 h at 0–10 °C. Iodobenzene was removed by extraction with CH_2Cl_2, and the aqueous layer on basification followed by extraction with CH_2Cl_2 (8 × 25 mL) gave 0.57 g (37%) of **2** mp 65–66 °C, after crystallization from hexane. In addition to **2**, tropan-3-one (**6**) was also recovered in about 50% yield.

Control Experiments. Hydrolysis of 2α-Hydroxytropan-3-one Oxime (8). 2α-Hydroxytropan-3-one oxime (**8**) (1.02 g, 0.006 mol) was treated with 50 mL of 3 N HCl for 3 h. The solution was made alkaline with an excess of solid sodium bicarbonate and then saturated with ammonium chloride. Extraction with five 25-mL portions of methylene chloride yielded 0.76 g of an oil, which, on crystallization from hexane, gave pure product, 0.65 g, mp 65–66 °C. Mixed melting point with pure **2** remained undepressed. NMR and IR data proved identical with that of **2**. Similarly, cleavage performed in concentrated HCl and acetone gave **2**.

Hydrolysis of Acetal 7 in Methanolic HCl. A solution of 1.0 g of the acetal (**7**) in 20 mL of dry methanol was cooled to 0 °C. Hydrogen chloride gas was bubbled into the solution, and the mixture was stirred at room temperature for 2 h. The solvent was evaporated at reduced pressure, and 20 mL of a saturated $NaHCO_3$ was added. The basic solution was then saturated with ammonium chloride and extracted with methylene chloride. Once again, **2** was isolated as the sole product.

Acknowledgment. We thank the U.S. Army for the support of this work under Contract Number DAMD-17-85-C-5190.