HPLC analyses, and Dr. M. J. Dagani for technical contributions.

Registry No. 1, 33369-26-5; 2, 33369-46-9; 3, 82875-55-6; 4, 33369-45-8; 5, 33369-47-0; 6, 55770-78-0; 7, 931-25-9; 8a, 87453-30-3; 8b, 62380-76-1; 8c, 87453-31-4; 9a, 87453-32-5; 9c, 87453-33-6; diethyl 1,3-acetonedicarboxylate, 105-50-0; 3-chloro-2-butanone, 4091-39-8; 1,2-dibromoethyl acetate, 24442-57-7; α-chloroacetophenone, 532-27-4.

Degradative Autoxidation of *N*-Acyl-3-piperidinones under Basic Conditions

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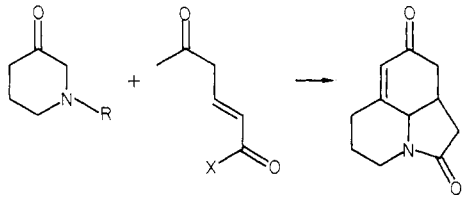
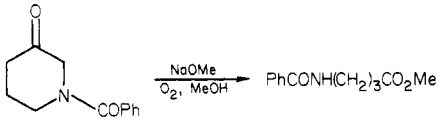
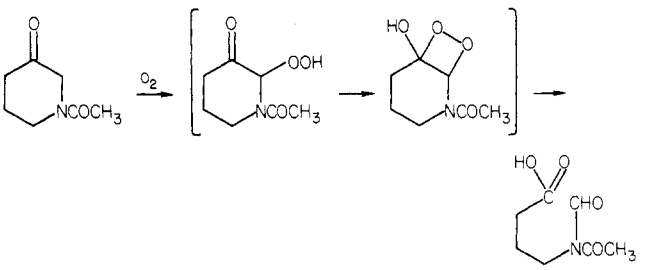
Base-catalyzed reactions of 3-piperidinones appear attractive in the synthesis of alkaloids. For example, the reaction of an appropriately substituted 3-piperidinone with a Michael acceptor could be a route to the hydrololidine ring system that is found in such alkaloids as lycorine, vinblastine, and aspidospermine. A base-catalyzed ring closure via a 3-pyrrolidinone (a five-membered analogue of a 3-piperidinone) was used in the synthesis of the lycorine skeleton.[2]



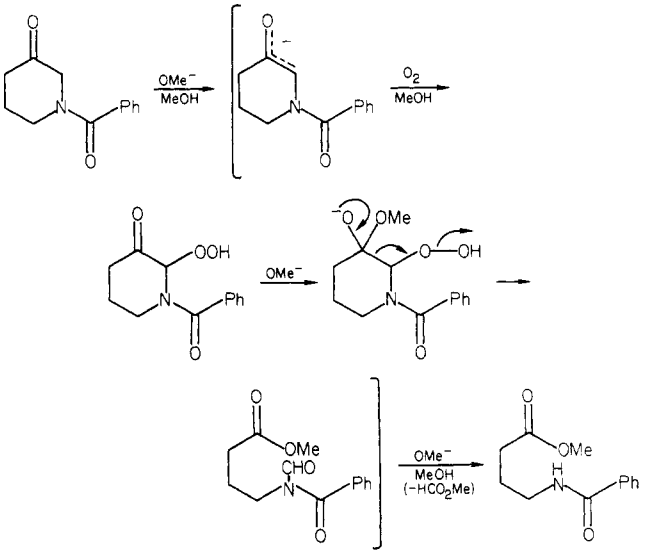
Treatment of a model compound, *N*-crotonyl-3-piperidinone, with sodium methoxide in methanol, potassium hydroxide in methanol, or Triton B in *tert*-butyl alcohol did not give the desired cyclization. A secondary amide was obtained in addition to unreacted starting material. The formation of a secondary amide also was observed in the attempted base-catalyzed cyclization of *N*-[5-(ethylenedioxy)-2-hexenoyl]-3-piperidinone or the base-catalyzed condensation of *N*-benzoyl-3-piperidinone with methyl crotonate. To determine the nature of the secondary amide products and how they might originate, we treated *N*-benzoyl-3-piperidinone with sodium methoxide in methanol at room temperature. Yields of up to 25% of methyl 4-benzamidobutanoate were obtained, the ester being identical with a sample prepared from 4-benzamidobutanoic acid.[3] The formation of this ester is arrested if air is excluded from the reaction. (In the absence of air essentially no reaction occurs at all with any of the derivatives.) When oxygen was bubbled through the reaction mixture a 95% yield of the ester was obtained.



The facile autoxidation of 3-piperidinones under neutral conditions has been reported and explained as possibly proceeding via an α-hydroperoxide and a 1,2-dioxetane.[4]



The above scheme cannot be followed in all details under the basic conditions we used because the methyl ester is obtained. In our system, a carbanion is a likely intermediate that reacts rapidly with oxygen to give the α-hydroperoxide or its anion. Deuterium exchange (0.3% NaOD, D_2O, 25 °C, 20 min) occurs to a greater extent at the 2-methylene group (80%) than at the 4-methylene group (37%) as determined from ^1H NMR spectra. The reaction of carbanions with oxygen has ample precedent.[5] It is reasonable to suppose that methoxide then adds to the 3-carbonyl group, resulting in the formation of methyl *N*-benzoyl-*N*-formyl-4-aminobutanoate, which is subsequently deformylated by methoxide ion as shown below. An analogous scheme was proposed to explain the base-catalyzed reaction in air of 1,2-diaza-2,5-dimethyl-6-phenylbicyclo[3.1.0]hept-6-ene-4-one with methanol.[6] Another possibility involves oxidation of the 2-position to a carbonyl group followed by attack of methoxide on the 3-carbonyl group to cause ring cleavage with loss of carbon monoxide. None of the 2,3-diketopiperidine derivative was observed although several stable examples of these compounds have been reported.[7] However, their rapid decomposition with methoxide ion is not precluded.



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(5) For examples, see the following: Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, 1731. Konen, D. A.; Silbert, L. S.; Pfeffer, P. E. *J. Org. Chem.* **1975**, *40*, 3253. Selikson, S. J.; Watt, D. S. *Ibid.* **1975**, *40*, 267. White, E. H.; Miano, J. D.; Umbert, M. *J. Am. Chem. Soc.* **1975**, *97*, 198. Reeb, R.; Vinchon, Y.; Riess, G.; Catala, J.-M.; Brossas, J. B. *Bull. Soc. Chim. Fr.* **1975**, 2717.
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(7) Ingold, C. K.; Shoppee, C. W. *J. Chem. Soc.* **1928**, 376. Polievktov, M. K.; Grigor'ev, A. B.; Smirnova, V. G.; Granik, V. G.; Glushkov, R. G. *Chem. Heterocycl. Compd.* **1973**, *9*, 529.

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Experimental Section

^{1}H NMR spectra were obtained on a Varian T-60 spectrometer. Mass spectra were obtained on a Perkin-Elmer Hitachi Model RMU-6E spectrometer. *N*-Benzoyl-3-piperidinone was prepared by oxidation of *N*-benzoyl-3-hydroxypiperidine.[8]

Reaction of Oxygen and Sodium Methoxide with *N*-Benzoyl-3-piperidinone. *N*-Benzoyl-1-3-piperidinone (1.0 g, 4.9 mmol) and sodium methoxide (0.27 g, 4.9 mmol) in methanol (100 mL) were stirred for 6.5 h at room temperature while oxygen was bubbled through the mixture. Acidification (5% HCl), extraction with methylene chloride (5 × 25 mL), drying ($MgSO_4$), and removal of the methylene chloride gave methyl 4-benzamidobutanoate[3] (1.03 g, 4.7 mmol, 95%), which was identical with an authentic sample prepared by treatment of the anion of 4-benzamidobutanoic acid with methyl iodide as described below. The ester was purified by chromatography on an alumina column with elution by chloroform: IR (thin film) 3322 (NH), 1739 (CO_2Me), 1639 (NHCOPh), 1538 (NHCOPh) cm^{-1}; NMR ($CDCl_3$) δ 7.85 (m, 2 H), 7.45 (m, 3 H), 7.1 (m, NH), 3.64 (s, 3 H), 3.48 (d, t, 2 H), 2.41 (t, 2 H), 1.97 (m, 2 H); EI-MS (70 eV), *m/e* (relative intensity) 221 (7), 134 (7), 116 (15), 105 (100), 77 (30); UV (95% EtOH) 227 nm.

In reactions where oxygen was not added deliberately but where air was present, yields of 7–25% of methyl 4-benzamidobutanoate were obtained with reaction times of up to 68 h.

Deuterium Exchange of *N*-Benzoyl-3-piperidinone. A solution of the piperidinone (0.05 g) in chloroform-*d* (0.5 mL) was shaken with solutions of sodium deuteroxide (0.1–13%) in deuterium oxide (0.5 mL) at ambient temperature. ^{1}H NMR spectra were taken at various time intervals. No deuteration was observed with 0.1% NaOD after 1 h. With 0.3% NaOD the C-2 protons exchanged more rapidly than the C-4 protons; after 20 min 80% deuteration at C-2 and 37% at C-4 was observed. Complete deuteration at both C-2 and C-4 was observed with concentrations of 5% or higher of NaOD. The infrared spectrum of the deuterated material showed a weak C–D stretching vibration at 2488 cm^{-1} and the ^{1}H NMR spectrum for the alkane protons was simplified: δ 3.72 (t, 2 H), 1.99 (t, 2 H). Both 2- and 4-methylene groups were deuterated by refluxing *N*-benzoyl-3-piperidinone in benzene with 1 equiv of sodium hydride for 2–20 h followed by addition of deuterium oxide. Apparently the deuteroxide that is formed catalyzes the exchange of all the protons adjacent to the 3-carbonyl group.

Methyl 4-Benzamidobutanoate. The methods used in this preparation differ from those reported previously.[3] 2-Pyrrolidinone (17 g, 0.20 mol) was refluxed with concentrated sulfuric acid (40 mL) in water (500 mL) for 2 h. The solution was made strongly alkaline with 40% aqueous sodium hydroxide. Benzoyl chloride (26 mL, 0.20 mol) was added to the cooled solution during 30 min. The solution was filtered and acidified to pH 3–5 by addition of concentrated hydrochloric acid. The white precipitate of 4-benzamidobutanoic acid (19 g, 0.09 mol, 46%) was filtered, washed twice with water, and dried. The acid (4.0 g, 0.019 mol), methyl iodide (4.0 g, 0.028 mol), and potassium carbonate (3.0 g, 0.026 mol) were stirred in methanol (20 mL) for 42 h at room temperature. The sample was filtered and the methanol removed. Water (10 mL) was added to the residue, and the mixture was extracted with methylene chloride (5 × 15 mL). The methylene chloride solution was dried ($MgSO_4$). Removal of the solvent yielded the ester (2.9 g, 0.013 mol, 69%). The properties of this ester were identical with those reported for the product of the reaction of *N*-benzoyl-3-piperidinone with oxygen and sodium methoxide.

Registry No. *N*-Benzoyl-3-piperidinone, 67452-85-1; methyl 4-benzamidobutanoate, 87461-71-0.

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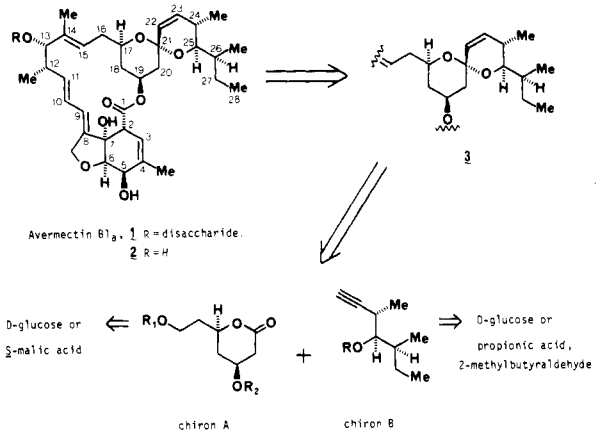
Communications

Stereocontrolled Synthesis of the Spiro Ketal Unit of Avermectin B_{1a} Aglycon

Summary: A stereocontrolled total synthesis of the 1,7-dioxaspiro[5.5]undecene subunit of the avermectin B_{1a} aglycon is presented based on the "chiron" approach which utilizes optically active starting materials.

Sir: The avermectins are a group of fermentation products of *Streptomyces avermitilis*, which possess potent anthelmintic and insecticidal activities.[1] Avermectin B_{1a} (1), the most active member of this family,[2] is a glycosidic derivative of a pentacyclic 16-membered lactone, which appears to act by interference with invertebrate neurotransmission.[3] In this paper, we report the total synthesis of the 1,7-dioxaspiro[5.5]undecane subunit **3** of avermectin B_{1a} aglycon **2** in optically pure form (Scheme I).

Scheme I



Two elegant syntheses of milbemycin B_3, an antibiotic which is structurally related but somewhat simpler in overall features compared to the avermectins, have been recently reported.[4,5] In one of these,[5] the antibiotic was

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