Monobenzyl 3-hydroxypentanedioic acid (5b) was prepared in 54% yield from monobenzyl acetone dicarboxylate by the procedure described above: mp 68–68.5 °C (recrystallized from EtAc–hexanes); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.49, (d, J = 6 Hz), 2.53 (d, J = 6 Hz) together 4 H, 4.47 (quintet, 1 H), 5.11 (s, 2 H), 6.56 (br s, 2 H), 7.33 (s, 5 H); IR ($CHCl_3$) 3500 (br), 1720 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.5; H, 5.92. Found: C, 60.28; H, 6.02.

Hydroxamates of 3-hydroxyglutaric acids (6) were prepared by the carbodiimide-mediated coupling of the acid and hydroxylamine described previously.[11]

Methyl *O*-benzyl-β-hydroxyglutaromonohydroxamate (6a) was obtained in 62.8% yield: mp 78–79 °C NMR ($CDCl_3$, 90 MHz) δ 2.29 (2 H, br d, J = 6 Hz), 2.48 (2 H, d, J = 6 Hz), 3.69 (3 H, s), 4.36 (2 H, quintet superimposed on a br s), 4.87 (2 H, s), 7.4 (5 H, s), 9.39 (1 H, br s); IR (KBr) 1720, 1680 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.38. Found: C, 58.32; H, 5.98; N, 5.24.

Benzyl *O*-benzyl-β-hydroxyglutaromonohydroxamic acid (6b) was prepared in 76% yield: mp 94.5–96 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.27 (2 H, br d), 2.5 (2 H, d, J = 6 Hz), 3.87 (1 H, br s), 4.37 (1 H, quintet, J = 6 Hz), 4.84 (2 H, br s), 5.1 (2 H, s), 7.38 (10 H, s), 9.29 (1 H, br s); IR (KBr) 3500 (br), 3150, 3000, 1715, 1660 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.55; H, 6.19; N, 3.88.

Benzyl *O*-pivaloyl-β-hydroxyglutaromonohydroxamic acid (6c) was prepared in 50% yield: mp 72.5–73.5 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) 1.32 (9 H, s), 2.5 (2 H, d, J = 6 Hz), 2.63 (2 H, d, J = 6 Hz), 4.17 (1 H, br s), 4.47 (1 H, quintet, J = 6 Hz), 4.17 (1 H, br s), 4.47 (1 H, quintet, J = 6 Hz), 5.13 (2 H, s), 7.39 (5 H, s), 8.39 (1 H, br s); IR (KBr) 3450, 3175, 2975, 1770, 1710, 1680 (s). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.65; H, 6.74; N, 4.22.

Azodicarboxylate-Mediated Cyclizations: General Procedures. The hydroxamic acid and the phosphorous compound R_3P (R = Ph, PhO, or a combination thereof, CH_3O, *i*-PrO) were dissolved in tetrahydrofuran (0.03–0.05 M) in a round-bottomed flask fitted with a Teflon stirbar and nitrogen inlet and outlet. After the solution was brought to the reaction temperature, diethyl azodicarboxylate was added dropwise via syringe over 1–2 min. Reactions were monitored by TLC (silica, 1:1 ethyl acetate/Skellysolve B) and quenched with 500–1000 mol % of water if olefin formation was observed by TLC. The reaction mixture was concentrated under reduced pressure and either chromatographed directly (ether–hexanes, CH_2Cl_2–hexanes or CH_2Cl_2–ether on silica gel) or first subjected to a cold aqueous workup that included basic (0.1 N NaOH) and acidic (0.5 M citric acid) extractions, followed by treatment with CH_2Cl_2–hexanes to remove most of the diethyl hydrazidodicarboxylate, and then chromatography.

***N*-(Benzyloxy)-4-[(methoxycarbonyl)methyl]-2-azetidinone (7a)** was prepared as an oil in 49.6% yield by the reaction of **6a** with $(PhO)_3P$ (500 mol %)/DEAD (125 mol %) for 16 h at room temperature: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.27–3.00 (m, 4 H, CH_2 of ring and $CH_2CO_2CH_3$), 3.68 (s, 3 H), 3.94 (m, 1 H), 4.93 (s, 2 H), 7.47 (s, 5 H).

***N*-(Benzyloxy)-4-[[(benzyloxy)carbonyl]methyl]-2-azetidinone (7b)** was prepared as an oil in 35% yield by the reaction of **6b** with $(PhO)_2PPh$/DEAE: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.27–2.97 (m, 4 H, CH_2 of the ring and CH_2CO_2R), 3.97 (m, 1 H), 4.90 (s, 2 H), 5.10 (s, 2 H), 7.37 and 7.41 (2 s, 10 H).

1-(Pivaloyloxy)-4-[[(benzyloxy)carbonyl]methyl]-2-azetidinone (7c) was prepared as an oil in 70% yield by the reaction of **6c** with $(PhO)_3P$/DEAD for 3–4 days at room temperature: ^{1}H NMR δ 1.30 (s, 9 H), 2.53–3.27 (m, CH_2CO_2R and CH_2 of the ring), 4.43 (dq, 1 H, J = 2 and 6 Hz), 5.2 (s, 2 H), 7.40 (s, 5 H); In the 300-MHz NMR, the multiplet between δ 2.53 and 3.27 is shown to be two sets of double doublets for the protons on C_3 and one doublet of quartets for the methylene protons of the C_4 substituent; IR ($CHCl_3$) 1805, 1765, 1735 cm^{-1}.

1-Hydroxy-4-[[(benzyloxy)carbonyl]methyl]-2-azetidinone (7, R^1 = H). Compound **7c** (142 mg, 0.445 mmol) was dissolved in 10 mL of THF–H_2O (1:1) and treated with 250 mg (730 mol %) of ammonium acetate. Acetone was added until the solution became homogeneous. The solution was stirred at room temperature for 12 h and then concentrated to remove the THF. The aqueous residue was adjusted to pH 9 with an aqueous 5% Na_2CO_3 solution and extracted with three 10-mL portions of ethyl acetate to remove any starting material (**7c**) and pivalamide. The aqueous layer was then acidified to pH 2 with 1.2 N HCl, saturated by the addition of solid NaCl, and extracted with five portions of ethyl acetate. These latter extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated to yield the *N*-hydroxy compound as an oil in 60% yield. This compound was used directly without further purification:[19] ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.30–3.10 (m, 4 H, CO_2CH_2Ph and CH_2 of the ring), 4.06 (dq, 1 H, J = 2 and 6 Hz, methine of the ring), 5.13 (s, 2 H), 7.38 (s, 5 H).

4-[[(Benzyloxy)carbonyl]methyl]-2-azetidinone (3). The *N*-hydroxy compound **7** (R^1 = H; 65 mg, 0.3 mmol) was dissolved in 5 mL of THF–H_2O (1:4). Nitrogen was bubbled through the solution and 3.0 mL of a 20% aqueous solution of $TiCl_3$ (Matheson Coleman and Bell) was added dropwise while maintaining the pH at 7 by automatic addition of 1 N NaOH with a pH stat. After stirring at room temperature for 1.5 h, the solution was purged with air and the resulting suspension was filtered through Celite. The Celite was washed with methanol. The filtrate and washings were combined, concentrated, and extracted with five 25-mL portions of ethyl acetate. The ethyl acetate layers were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated to yield 30 mg (50%) of **3** as an oil. Crystallization from ethyl acetate–hexanes gave 16 mg of **3** as white crystals: mp 92–92.5 °C (lit.[8c] mp 95 °C, from benzene); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.50–2.80 and 3.0–3.3 (m, 4 H, CH_2 of ring and CH_2CO_2Bz), 3.97 (dq, 1 H, methine of ring), 5.13 (s, 2 H), 6.13 (br s, NH), 7.4 (s, 5 H).

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Registry No. **3** (R = CH_2Ph), 81019-86-5; **5a**, 87118-53-4; **5b**, 87395-67-3; **6a**, 87395-68-4; **6b**, 87395-69-5; **6c**, 87395-70-8; **7a**, 87395-71-9; **7b**, 87395-72-0; **7c**, 87395-73-1; **7** (R = CH Ph; R^1 = H), 87395-74-2; (*E*)-**9c**, 87395-75-3; (*Z*)-**9c**, 87395-76-4; monomethyl acetonedicarboxylate, 78315-99-8; glutaconic anhydride, 5926-95-4; monobenzyl acetonedicarboxylate, 87395-77-5.

(19) Several related *N*-hydroxy compounds have a tendency to rearrange while heating in solvents during attempted recrystallization: Hirose, T.; Chiba, K.; Mishio, S.; Nakano, J.; Uno, H. *Heterocycles* **1982**, *19*, 1019.

Selective Hydrolysis–Decarboxylation of Ethyl 1,4-Dimethyl-3-(ethoxycarbonyl)-1*H*-pyrrole-2-acetate

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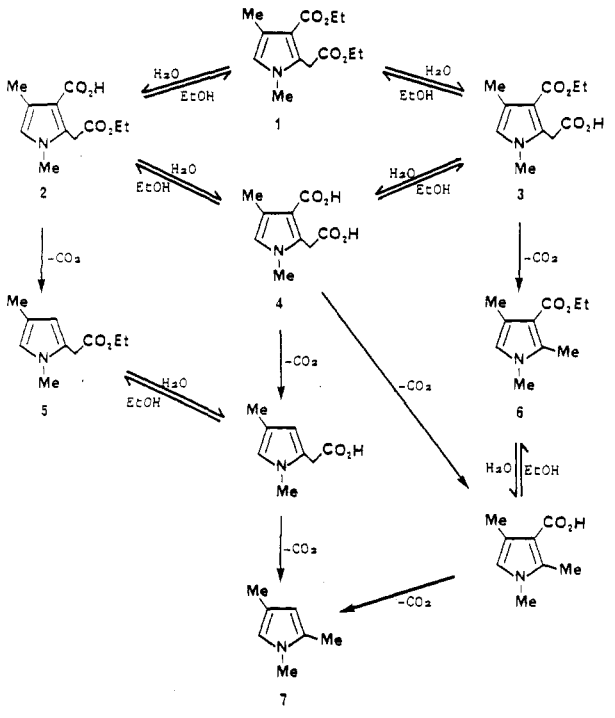
The conversion of title compound **1** to ethyl 1,4-dimethyl-1*H*-pyrrole-2-acetate (**5**) is an important transformation in the synthesis of 5-benzoyl-1,4-dimethyl-1*H*-pyrrole-2-acetic acid antiinflammatory agents.[1] Carson and Wong[1] described a three-step method in which diester **1** is hydrolyzed to diacid **4** with 25% NaOH, **4** is selectively reesterified to acid ester **2** with 0.5% HCl in ethanol, and

(1) Carson, J. R.; Wong, S. *J. Med. Chem.* **1973**, *16*, 172.

0022-3263/83/1948-4423$01.50/0

Scheme I



2 is decarboxylated at 200 °C to ester 5. Our attempts to simplify this sequence have resulted in a procedure by which selective hydrolysis and decarboxylation of the 3-carbethoxy group of 1 can be effected in a single operation in good yield.

Decarboxylation of pyrrole acids can be accomplished in several ways, such as pyrolysis, heating with copper bronze or copper chromite, or distillation from dilute alkaline or acidic solutions.[2] There are also isolated examples of direct removal of carboalkoxy groups.[3] Selective elimination of a pyrrole 3-carbethoxy function was reported by Chu and Chu,[4] who hydrolyzed 2,4-dimethyl-3,5-dicarbethoxy-1*H*-pyrrole preferentially at the 3-position with use of 85% sulfuric acid and decarboxylated the resulting acid ester.

Kinetic evidence suggests that the mechanism of acid-catalyzed ester hydrolysis is $A_{AC}2$ in dilute acid, but is $A_{AC}1$ in more concentrated (>85%) acid.[5] The $A_{AC}1$ mechanism involves an acylium ion intermediate, which should be generated more readily at the 3-position of pyrrole 1 than on the alkyl side chain. Therefore, hydrolysis of the 3-carbethoxy group should be favored in concentrated acid systems.

Treatment of diester 1 with various concentrations of sulfuric acid (82% to fuming) followed by isolation and heating of the neat product mixtures at 200 °C for 15 min afforded mixtures of compounds 1 and 5–7. In no case was the yield of desired compound 5 greater than about 10% by GC analysis.

Since reaction of diacid 4 with acidic ethanol results in selective esterification of the acetate carboxy group,[1] we tested addition of ethanol to the sulfuric acid systems and found that 1 could be converted directly to a mixture of the decarboxylated compounds 5–7. Product distribution was shown to be highly dependent on reagent composition. Optimum conditions involved treatment of 1 with a 10:9:1

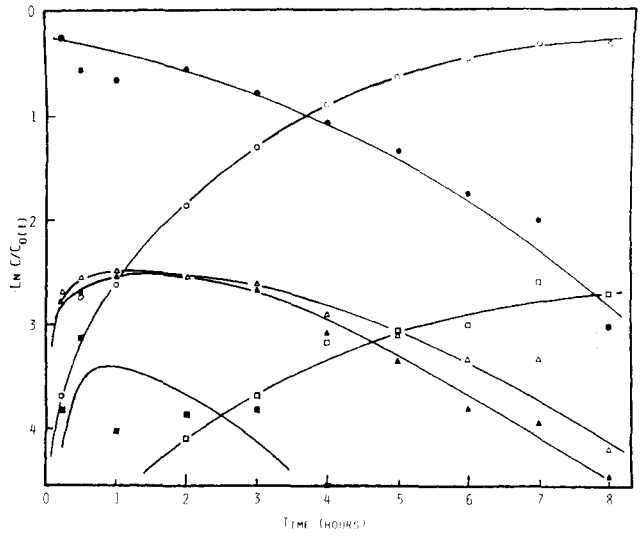
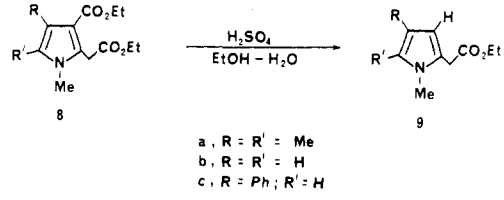


Figure 1. Hydrolysis–decarboxylation of 1 at 60 °C in $H_2SO_4/C_2H_5OH/H_2O$: (●) 1, (○) 5, (▲) 2, (△) 3, (■) 6, (□) 7.

Scheme II



volume ratio of 96% sulfuric acid/ethanol/water at 80 °C for 1 h, which afforded a 78% analytical yield of desired pyrrole 5.

Treatment of compound 2, 3, or 4 under the conditions described also afforded ester 5. Thus the reaction pathway can be envisioned as a series of hydrolysis–esterification equilibria followed by decarboxylations to produce compound 5 and the completely decarboxylated pyrrole 7 (Scheme I). To confirm this sequence, a mixture of diester 1, sulfuric acid, ethanol, and water maintained at 60 °C was sampled regularly, and the samples were analyzed by both GC and HPLC. Compounds 1–3 and 5–7 were observed in the reaction mixture; the relative amount of each present as the reaction progressed is shown in Figure 1. The preponderance of ester 5 indicates that either acid ester 2 is decarboxylated much faster than its isomer 3 and diacid 4, or the equilibrium mixture contains only small amounts of 3 and 4. Although pyrroles are known to undergo acid-catalyzed dimerization by attack of the protonated cation on the neutral species,[6] ester 5 appears to be quite stable under these conditions. The same yield of 5 was obtained after 4 or 24 h at 60 °C. Presumably extensive protonation of the pyrrole in this concentrated acid system inhibits dimerization.

Three other pyrrole diesters (8a–c) were synthesized to determine the effect of substituent changes on the hydrolysis–decarboxylation reaction (Scheme II). Only the 4-substituted analogues 1, 8a, and 8c gave good yields of decarboxylated products. Compound 8b was almost completely consumed but gave only 8% of desired product 9b.[7] Decarboxylation of aromatic acids is known to be accelerated by the presence of electron-donating groups in the ortho and para positions.[8] In addition, steric strain relief

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may be a factor as in the hydrolysis of methyl mesitoate in strong acid media.[9] It is reasonable to expect that similar electronic and steric factors influence pyrrole acid decarboxylations.

The hydrolysis–decarboxylation reaction can be carried out with other acids. Phosphoric acid and perchloric acid also converted compound 1 to compound 5. Hydrochloric acid was not effective. Diesters 1 and 8c were recovered in high yield after treatment for 1 h at 75–80 °C with ethanol saturated with hydrogen chloride.

Experimental Section

Melting points were determined with a Fischer-Johns hot stage or a Mel-Temp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane. Mass spectra were obtained on a Finnigan 4023 gas chromatograph/mass spectrometer equipped with a 50-m SE-52 fused silica capillary column. GC analyses were performed on a Hewlett-Packard 5380A instrument equipped with either a 10 ft × $^1/_8$ in. stainless steel column packed with 10% DEGS on Chromosorb Q or a 6 ft × $^1/_8$ in. stainless steel column packed with 10% SE-52 on Chromosorb W, using dibutyl phthalate as an internal standard. HPLC analyses were performed on a Waters M6000A instrument equipped with a 4.6 mm × 30 cm column packed with 10 μm silica and connected to a Schoeffel SF770 variable-wavelength detector set at 254 nm. The eluent solution was 97% dichloromethane, 2.5% acetic acid, and 0.5% methanol (volume percent). Elemental analyses were performed by Huffman Laboratories, Inc., Wheat Ridge, CO.

Conversion of Ethyl 1,4-Dimethyl-3-(ethoxycarbonyl)-1*H*-pyrrole-2-acetate (1) to Ethyl 1,4-Dimethyl-1*H*-pyrrole-2-acetate (5) with Sulfuric Acid. General Procedure. To a mixture of 2.0 g (7.9 mmol) of diester 1,[1] 4.6 mL of absolute ethanol, and 0.4 mL of water was added, dropwise, with stirring, 4.4 mL of 96% sulfuric acid. The solution was placed in a 75–80 °C oil bath, vigorously stirred for 75 min, and then poured into 15 mL of water. The resulting aqueous mixture was extracted with four 10-mL portions of dichloromethane. The organic layers were combined, dried ($MgSO_4$), concentrated, and distilled (short path, 95–100 °C, 1 torr) to give 1.0 g (71% yield) of colorless oil 5.

Analysis of the Reaction Mixture in the Conversion of 1 to 5. To 5.0 g (20 mmol) of diester 1 were added 3.5 mL of absolute ethanol and 5.4 mL of 96% sulfuric acid. This mixture was placed in a 60 °C oil bath and stirred vigorously. At intervals a portion of the reaction mixture was removed, weighed (about 0.4 g/portion), and partitioned between water and dichloromethane. The organic layers were dried ($MgSO_4$), concentrated, weighed, and analyzed. The amounts of compounds 5–7 were determined by GC (internal standard), and the amounts of compounds 1–3 were determined by HPLC (external standard). The results are summarized in Figure 1.

3-(Ethoxycarbonyl)-1,4-dimethyl-1*H*-pyrrole-2-acetic Acid (3). A mixture of 2.3 g (9.25 mmol) of 1, 1.4 g (10 mmol) of potassium carbonate, 25 mL of 95% ethanol, and 50 mL of water was heated at reflux for 16 h and poured into ice water. The resulting aqueous solution was acidified with 6 N HCl and the precipitated solid was collected by filtration, washed with water, and dried in vacuo at 50 °C to give 1.6 g (79% yield) of acid ester 3: mp 154–155 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3 H, J = 7 Hz), 2.20 (s, 3 H), 3.60 (s, 3 H), 3.99 (s, 2 H), 4.38 (q, 2 H, J = 7 Hz), 6.40 (s, 1 H), 10.5 (br s, 1 H).

Decarboxylation of a sample of this material at 200–210 °C for 20 min afforded 3-(ethoxycarbonyl)-1,2,4-trimethyl-1*H*-pyrrole (6).[10]

Conversion of Ethyl 3-Carboxy-1,4-dimethyl-1*H*-pyrrole-2-acetate (2) to 5. By the general procedure 0.10 g (0.44 mmol) of acid ester 2[1] afforded 77 mg of a product mixture that contained, by GC analysis, 58 mg (70% yield) of ester 5.

Conversion of 3 to 5. By the general procedure 0.10 g (0.44 mmol) of acid ester 3 afforded 77 mg of a product mixture that contained, by GC analysis, 43 mg (53% yield) of ester 5, 11 mg (23% yield) of 1,2,4-trimethyl-1*H*-pyrrole (7),[11] and 2 mg (1% yield) of 1.

Conversion of 3-Carboxy-1,4-dimethyl-1*H*-pyrrole-2-acetic Acid (4) to 5. By the general procedure 2.7 g (15 mmol) of diacid 4[1] afforded a product mixture that contained, by GC analysis, 2.3 g (84% yield) of ester 5, 0.1 g (7% yield) of 7, and 0.2 g (6% yield) of 1.

Ethyl 3-(Ethoxycarbonyl)-1,4,5-trimethyl-1*H*-pyrrole-2-acetate (8a). A solution was prepared from 10 g (51 mmol) of diethyl 1,3-acetonedicarboxylate, 8.3 g (77 mmol) of 3-chloro-2-butanone, and 45 g of dichloromethane. This solution was added simultaneously with 35 g of 40% aqueous methylamine (0.45 mol) to a 100-mL flask equipped with a distilling head during a 15-min period. The resulting mixture was heated to 90 °C for 30 min to remove the methylamine and dichloromethane, cooled, and extracted with 45 g of toluene in two portions. The extracts were dried ($MgSO_4$) and concentrated at 60 °C. The solid residue crystallized from methanol to give 3.4 g (25% yield) of 8a: mp 85–87.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7 Hz), 1.32 (t, 3 H, J = 7 Hz), 2.11 (s, 3 H), 2.19 (s, 3 H), 3.42 (s, 3 H), 4.09 (s, 2 H), 4.19 (q, 4 H, J = 7 Hz), 4.26 (q, 4 H, J = 7 Hz); mass spectrum (70 eV), m/e (relative intensity) 267 (M^+, 20), 222 (10), 221 (28), 194 (87), 192 (14), 166 (60), 150 (6), 121 (8), 56 (100), 42 (7). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.88; H, 7.87; N, 5.30.

Conversion of 8a to Ethyl 1,4,5-Trimethyl-1*H*-pyrrole-2-acetate (9a). By the general procedure 3.0 g (11 mmol) of diester 8a afforded a product mixture that was distilled (short path, 95–100 °C, 1.0–1.5 torr) to give 1.4 g (64% yield) of ester 9a: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 8 Hz), 1.93 (s, 3 H), 2.05 (s, 3 H), 3.33 (s, 3 H), 3.50 (s, 2 H), 4.10 (q, 2 H, J = 8 Hz), 5.77 (s, 1 H); mass spectrum (70 eV), m/e (relative intensity) 195 (M^+, 21), 123 (6), 122 (100), 56 (5). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.65; H, 8.78; N, 7.18. Found: C, 67.07; H, 8.71; N, 7.24.

Ethyl 3-(Ethoxycarbonyl)-1-methyl-1*H*-pyrrole-2-acetate (8b). By a procedure analogous to that of Bisagni et al.,[12] 62 g (0.30 mol) of 15% aqueous methylamine, 12 g (0.05 mol) of 1,2-dibromoethyl acetate,[13] and 10 g (0.05 mol) of diethyl 1,3-acetonedicarboxylate afforded 3.1 g (26% yield) of diester 8b.[14]

Ethyl 3-(Ethoxycarbonyl)-1-methyl-4-phenyl-1*H*-pyrrole-2-acetate (8c). This compound was prepared from α-chloroacetophenone by the procedure described for synthesis of diester 8a. It was concentrated by column chromatography on silica gel with dichloromethane as eluent and isolated as a crude brown oil by preparative TLC (silica gel) in about 12% yield.[15] The ^{1}H NMR spectrum was consistent with structure 8c. Mass spectrum (70 eV), m/e (relative intensity) 315 (M^+, 28), 270 (8), 269 (74), 242 (63), 241 (87), 214 (100), 168 (11), 128 (3), 42 (66).

Conversion of 8c to Ethyl 1-Methyl-4-phenyl-1*H*-pyrrole-2-acetate (9c). By the general procedure 23 g (7.5 mmol) of crude diester 8c afforded a product mixture that contained, by GC analysis, ester 9c and no trace of unreacted diester 8c. Compound 9c was isolated as a crude brown oil (1.2 g, 51% yield). The ^{1}H NMR spectrum was consistent with structure 9c. Mass spectrum (70 eV), m/e (relative intensity) 243 (M^+, 30), 171 (8), 170 (100), 128 (8), 42 (22).

Acknowledgment. We thank Dr. V. O. Brandt for obtaining mass spectra, T. W. McKay for carrying out

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(15) The 5-isomers (normal Hantzch pyrrole synthesis products) were always produced in minor amounts. Attempts to separate 8c from the 5-phenyl isomer (about 10% of the mixture) by recrystallization were unsuccessful. However, the two isomers can be differentiated by their mass spectra. The pyrrole unsubstituted at position 5 always gives the characteristic CH_3NCH^+ ion (m/e 42) in abundance. This fragment is lacking or observed in low abundance in 1-methylpyrroles substituted at the α positions.

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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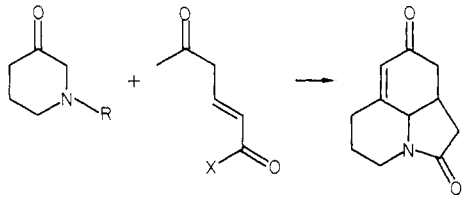
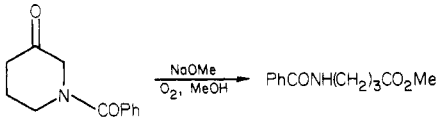
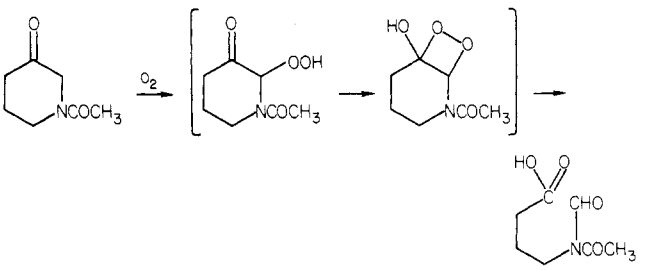
Base-catalyzed reactions of 3-piperidinones appear attractive in the synthesis of alkaloids. For example, the reaction of an appropriately substituted 3-piperidinone with a Michael acceptor could be a route to the hydrololidine ring system that is found in such alkaloids as lycorine, vinblastine, and 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]



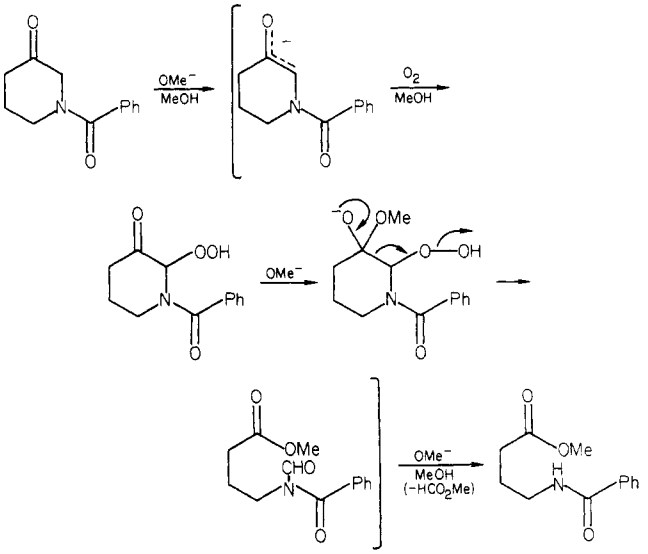
Treatment of a model compound, *N*-crotonyl-3-piperidinone, with sodium methoxide in methanol, potassium hydroxide in methanol, or Triton B in *tert*-butyl alcohol did not give the desired cyclization. A secondary amide was obtained in addition to unreacted starting material. The formation of a secondary 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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