Oxidation of α-Ketoacyl Derivatives. Rearrangement of Pyruvates to Malonates[1]

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Abstract: α-Keto esters and amides undergo oxidative rearrangement when treated with periodate at pH 7–9 to give malonic acid derivatives. When the amide is cyclic (α-ketolactams), ring contraction occurs. The major pathway of this oxidative rearrangement of α-ketoacyl derivatives probably involves the cleavage of an intermediate α-hydroxycyclopropanone to give the observed product. In addition, a minor path through a cyclopropanedione has been invoked to rationalize the data obtained with carbon-14 labeled compounds.

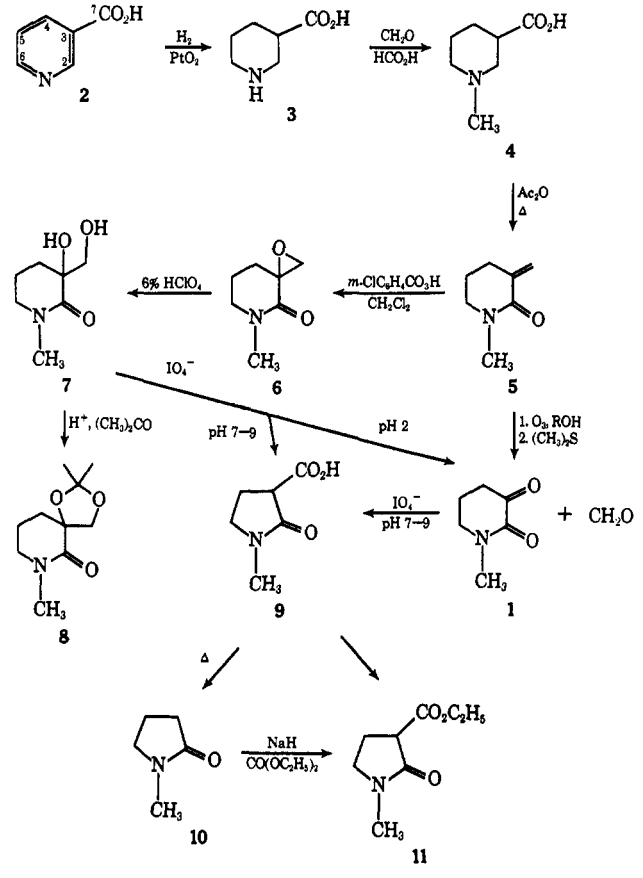
In a preliminary communication,[3] we reported the oxidative rearrangement of α-ketoacyl derivatives. We now provide the complete experimental details of this work and additional observations concerning both the scope of the reaction and the proposed mechanism.

Scope. The oxidative rearrangement of α-ketoacyl derivatives with periodate has been established in the present experiments to include both acyclic and cyclic α-keto esters and amides. The synthesis of the specific α-ketoacyl derivatives examined and the characterization of their respective skeletal rearrangement products is presented in the following.

The cyclic α-ketoamide, 1-methyl-2,3-piperidinedione (**1**), was synthesized as shown in Scheme I. Nicotinic acid (**2**) was catalytically hydrogenated to quantitatively give **3**. Reductive methylation of **3** gave 1-methylnipecotic acid (**4**),[4] in quantitative yield, and **4** in refluxing acetic anhydride gave 1-methyl-3-methylene-2-piperidone (**5**)[5] in 93% yield. Epoxidation of **5** with *m*-chloroperbenzoic acid in methylene chloride gave an 88% yield of **6** which on hydrolysis with 6% perchloric acid[6] quantitatively gave **7**, characterized further by conversion to the acetonide derivative **8**. Periodate oxidation of **7** in dilute acid gave dione **1** (83%). Alternately, ozonolysis of **5** at −78° in an alcoholic solvent followed by addition of either trimethoxyphosphine[7] or dimethyl sulfide[8] gave **1** in 65% yield. Although longer, the former procedure was preferable because of greater ease in purification. The phenylhydrazone **12** of **1** was prepared for comparison purposes and found to be identical with a sample of **12** obtained *via* phenyldiazonium salt coupling with 3-carboxy-1-methyl-2-piperidinone (**13**).

Although oxidation of glycol **7** with excess periodate at pH 2 gave piperidinedione **1** and formaldehyde (characterized by reaction with chromotropic acid[9] and conversion to the dimedone derivative[10]), the reaction

Scheme I



of either **1** or **7** with excess periodate at pH 7 or 9 for 10 hr gave an 80% yield of 3-carboxy-1-methyl-2-pyrrolidinone (**9**), unambiguously characterized by decarboxylation to 1-methyl-2-pyrrolidinone (**10**). In addition, **9** was identical with an authentic sample of 3-carboxy-1-methyl-2-pyrrolidinone prepared by hydrolysis of the corresponding ethyl ester **11**, synthesized by condensation of 1-methyl-2-pyrrolidinone (**10**) with diethyl carbonate.[11]

The oxidative rearrangement reaction was next applied to *N,N*-dimethyl-2-oxobutanamide (**14**) which in aqueous periodate at pH 9 gave a 69% yield of *N,N*-dimethylmethylmalonamic acid (**15**) identical with an

(1) This work was supported in part by Grant No. MH12797 from the National Institute of Mental Health, U. S. Public Health Service.
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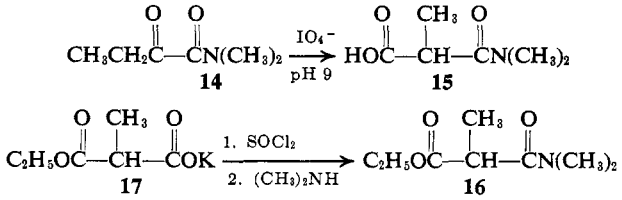
(11) M. L. Rueppel and H. Rapoport, *ibid.*, **92**, 5528 (1970); **93**, 7021 (1971).

authentic sample prepared by hydrolysis of ethyl *N,N*-dimethylmethylmalonamate (**16**).[12] Substitution on



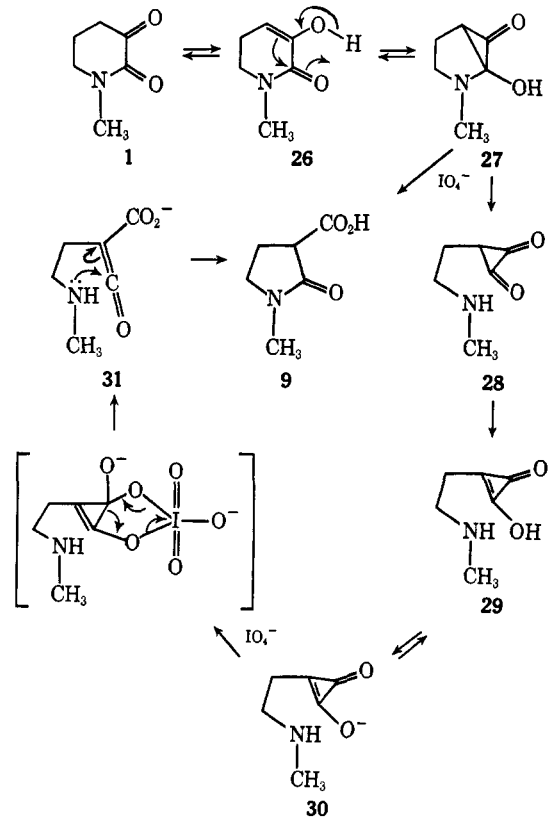
the nitrogen was shown to be unnecessary by application of the rearrangement reaction to 2-oxoheptanamide (**18**) prepared from the 2-oxoheptanoic acid (**19**). The acid **19** was obtained by hydrolysis of the intermediate ethyl 2-ethoxalylhexanoate which was prepared by condensation of ethyl hexanoate with diethyl oxalate. Periodate oxidation of amide **18** with aqueous periodate at pH 9 for 20 hr gave butylmalonamic acid (**20**) in 19% yield. Although no attempt has been made to optimize the yield of rearrangement product, the above clearly indicates a broad synthetic application for this rearrangement reaction to N-substituted and N-unsubstituted α-ketoamides.

The oxidative rearrangement of α-keto esters has been examined with the ethyl and *tert*-butyl esters of 2-oxobutanoate. Periodate oxidation of ethyl 2-oxobutanoate (**21**) at pH 7 followed by addition of ethereal diazomethane yielded methyl propionate, methyl ethyl methylmalonate (**23**), and methyl ethyl methylhydroxymalonate (**24**). Methyl propionate (corresponding to propionic acid) resulted from hydrolysis of ethyl 2-oxobutanoate (**21**) and subsequent periodate oxidation[13] of 2-oxobutanoic acid. Methyl ethyl methylmalonate (**23**), the expected esterified rearrangement product, was characterized by comparison to an authentic sample. The hydroxymalonate **24** was isolated in 17% yield; **24** is presumably formed by further oxidation of ethyl hydrogen methylmalonate,[14] the expected rearrangement product. We have found that potassium ethyl methylmalonate undergoes periodate oxidation[15] at pH 7; however, no detectable oxidation was found at pH 9 over the same period of time.

In order to develop the rearrangement of α-keto esters into a synthetic method for preparing half-esters and unsymmetrical esters of substituted malonic acids, *tert*-butyl 2-oxobutanoate (**22**) was subjected to the oxidative rearrangement. The *tert*-butyl ester was selected to minimize losses due to hydrolysis and to permit carrying out of the oxidation at pH 9 to avoid overoxidation of the expected product. In accord with these expectations, oxidation of *tert*-butyl 2-oxobutanoate (**22**) with periodate at pH 9 afforded *tert*-butyl hydrogen methylmalonate (**25**) in 67% yield.[16] Clearly, the above experiments indicate synthetic utility for the oxidative rearrangement of α-keto esters to malonate derivatives.

Mechanism. Concurrently with the study of the scope of the periodate oxidative rearrangement reaction its mechanism has been examined. Most of these studies have been based on 1-methyl-2,3-piperidinedione as the prototype although an analogous mechanism can be written for any of the other compounds examined and a cyclic structure is not required. The complete postulated mechanism for oxidative rearrangement is shown in Scheme II and the experimental evidence for it is presented below.

Scheme II



According to the postulated mechanism, 1-methyl-2,3-piperidinedione (**1**) is assumed to be in equilibrium with its enol **26**, which is then postulated to undergo intramolecular nucleophilic attack at its amide carbonyl to give the cyclopropanone **27**. The cyclopropanone **27** should be capable of reverting to the enol **26**; however, **27** has two other modes of reaction. First, as an α-hydroxy ketone and according to the known oxidation of α-hydroxy ketones with periodate, **27** would give the observed product **9**.[17,18] The evidence which is given below clearly indicates that the major reaction mode to give **9** is by oxidation of **27**.

A second reaction path becomes apparent since **27** is also a carbinolamine. Opening of **27** *via* the carbinolamine would give the cyclopropanedione **28**, and evidence for the participation of **28** is based on labeling experiments to be described. The cyclopropanedione **28** would be expected to exist completely in its enol form **29** since phenylhydroxycyclopropenone has been reported to show no evidence for the phenylcyclopropanedione tautomer.[19] Under the conditions of the periodate reaction at pH 7 or 9, **28** should be completely converted to its anion **30**, in analogy with phenylhydroxycyclopropenone for which a pK_a of 2.0 ± 0.5 has been reported[19] in agreement with the predicted

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(13) D. B. Sprinson and E. Chargraff, *J. Biol. Chem.*, **164**, 433 (1946).
(14) C. F. Huebner, S. R. Ames, and E. C. Bubl, *J. Amer. Chem. Soc.*, **68**, 1621 (1946).
(15) J. R. Clamp and L. Hough, *Biochem. J.*, **94**, 17 (1965).
(16) Experiments by D. R. Bender, this laboratory.
(17) B. Sklarz, *Quart. Rev., Chem. Soc.*, **21**, 3 (1967).
(18) C. A. Bunton and V. J. Shiner, *J. Chem. Soc.*, 1593 (1960).
(19) D. G. Farnum and P. E. Thurston, *J. Amer. Chem. Soc.*, **86**, 4206 (1964); D. G. Farnum, J. Chickos and P. E. Thurston, *ibid.*, **88**, 3075 (1966).

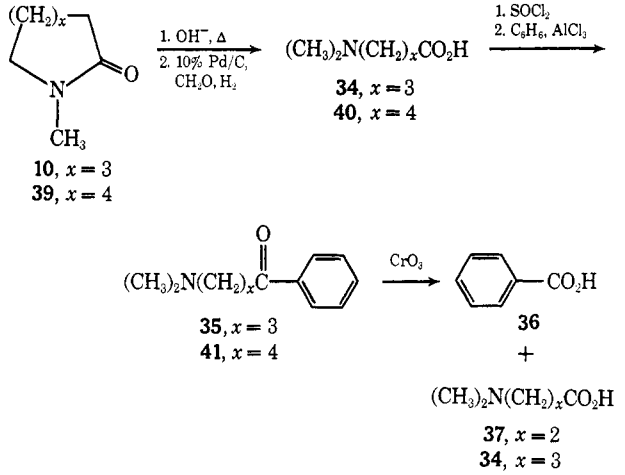
value of 2.0 for hydroxycyclopropenone.[20] Periodate oxidation of **30** would be expected to give the ketene intermediate **31** based upon the known mode of cleavage of α-hydroxy ketones.[18] Periodate acts as a mixed nucleophilic and electrophilic reagent in cleaving α-hydroxy ketones; the oxygen atom becomes linked to the carbonyl carbon while the hydroxyl oxygen becomes linked to the iodine atom. Subsequent collapse normally gives an acid and an aldehyde or ketone; analogous reaction of **30** would be expected to give the carboxyketene intermediate **31**. The ketene **31** would then undergo intramolecular nucleophilic attack to give the observed product **9**. The pathway of formation of **9** *via* **28**, **29**, **30**, and **31** is postulated as a consequence of labeling studies with carbon-14; this pathway during a normal oxidation is a minor route (~1.0%).

Evidence for the postulated mechanism of the periodate oxidative rearrangement first was acquired using 3-hydroxy-3-hydroxymethyl-1-methyl-2-piperidone-*2*-^{14}C (**7**) synthesized from nicotinic acid-*7*-^{14}C (**2**)[21] as shown in Scheme I. The carboxyl carbon (C-7) of nicotinic acid becomes C-2 of **7** during its preparation. Thus **7**-*2*-^{14}C [specific activity 141,300 dpm/mmol (100.0%)] was obtained from nicotinic acid-*7*-^{14}C of the same specific activity. Periodate oxidation of **7**-*2*-^{14}C at pH 9 for 16 hr gave 3-carboxy-1-methyl-2-pyrrolidinone and formaldehyde; the formaldehyde formed showed <0.02% of the activity. According to the mechanism in Scheme II, if 3-carboxy-1-methyl-2-pyrrolidinone (**9**) were formed only by direct oxidation of **27**, all the activity of **7**-*2*-^{14}C should be in the C-2 (amide carbonyl) of **9**; however, this was found not to be the case. Decarboxylation of **9** gave 1-methyl-2-pyrrolidinone [specific activity 140,100 dpm/mmol (99.2%)] and CO_2 [as $BaCO_3$, specific activity 853 dpm/mmol (0.6%)]. The activity in the CO_2 clearly exceeded experimental error and indicated some scrambling of label during the oxidation.

The possibility that the observed scrambling was a result of partial hydrolysis of **9** to give 2-methylaminoethylmalonic acid (**32**) during the reaction or isolation followed by reclosure of **32** to **9** was examined; however, the intermediacy of **32** has been conclusively eliminated. A sample of the 3-carboxy-1-methyl-2-pyrrolidinone (**9**), an aliquot of which had been previously decarboxylated, was resubmitted to the identical reaction and isolation conditions. Subsequent decarboxylation gave 1-methyl-2-pyrrolidinone and CO_2 with the same specific activities as previously. Therefore, the observed scrambling must be a consequence of the mechanism of the reaction and not a function of any subsequent reaction of **9**. This was further substantiated by the preparation of **32** by alkaline hydrolysis of 3-ethoxycarbonyl-1-methyl-2-pyrrolidinone (**11**); **32** was not isolated, but was characterized from an aliquot by conversion to its *p*-bromobenzenesulfonamide derivative. When the solution of 2-methylaminoethylmalonate (**32**) was acidified to pH 2, no detectable ring closure of **32** to **9** occurred in a period of 4 days. The postulation of a minor path *via* the cyclopropanedione **28**, however, accounts for the observed scrambling.

As required by Scheme II, all the activity of the 1-methyl-2-pyrrolidinone (**10**), formed by decarboxylation of **9**, was at C-2 (the amide carbonyl); this was established by degradation of **10** (Scheme III). 1-

Scheme III



Methyl-2-pyrrolidinone [specific activity 140,100 dpm/mmol (100.0%)] was hydrolyzed in alkali to give sodium 4-methylaminobutanoate (**33**) which was reductively methylated at pH 7 to give 4-dimethylaminobutanoic acid (**34**) in 85% overall yield. The acid **34** [specific activity 140,100 dpm/mmol (100.0%)] was converted to the phenyl ketone, γ-dimethylaminobutyrophenone (**35**), in 98% yield and the latter was then oxidized with chromic acid to give benzoic acid (**36**) and *N*,*N*-dimethyl-β-alanine (**37**) in 65 and 63% yield, respectively. The benzoic acid, within experimental error, contained all the activity, demonstrating that C-2 was the sole radioactive carbon of **10**.

Additional evidence for the intermediacy of the symmetrical cyclopropanedione **28** in the formation of 3-carboxy-1-methyl-2-pyrrolidinone (**10**) from 1-methyl-2,3-piperidinedione (**1**) was obtained by first oxidizing 3-hydroxy-3-hydroxymethyl-1-methyl-2-piperidone-*2*-^{14}C [specific activity 141,300 dpm/mmol (100.0%)] at pH 2 with aqueous periodate to give 1-methyl-2,3-piperidinedione-*2*-^{14}C (**1**). The dione **1** was then dissolved in a pH 9 aqueous buffer at room temperature in the absence of periodate. After 53 hr, periodate was added, and oxidation was allowed to proceed for 10 hr; isolation gave **9** [specific activity 139,500 dpm/mmol (98.7%)]. Decarboxylation of **9** gave 1-methylpyrrolidinone [specific activity 112,500 dpm/mmol (79.6%)] and CO_2 [specific activity 26,600 dpm/mmol (18.8%)]. Clearly, increased scrambling was observed in **9** as a result of the extended period at pH 9 without oxidant. Similarly, when **1** was treated at room temperature in a pH 9 buffer for 27 hr before oxidation, and **9** was then isolated and decarboxylated, 1-methyl-2-pyrrolidinone [specific activity 119,400 dpm/mmol (84.5%)] and CO_2 [specific activity 20,200 dpm/mmol (14.3%)] were obtained. Direct oxidation of 1-methyl-2,3-piperidinedione-*2*-^{14}C (**1**) in pH 9 buffer saturated with sodium

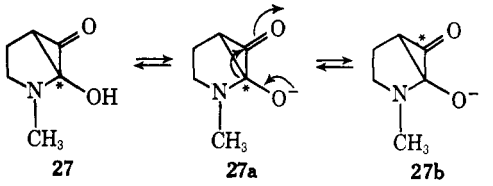
(20) E. J. Smutny, M. C. Caserio, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 1793 (1960); R. West and D. L. Powell, *ibid.*, **85**, 2577 (1963).

(21) Purchased from International Chemical and Nuclear Corporation. Purity was established by thin-layer chromatography and radioautography and integrity of label at C-7 of nicotinic acid was established by conversion to 3-benzoylpyridine [F. J. Villani and M. S. King, *Org. Syn.*, **37**, 6 (1957)], then to a mixture of stereoisomeric phenyl 3-pyridylketoximes, mp 135–155° [B. Jeiteles, *Monatsh.*, **17**, 575 (1896)] which was Beckmann rearranged using thionyl chloride. Hydrolysis of the rearranged products gave benzoic acid and nicotinic acid, both of equal specific activity, and 3-aminopyridine and aniline, both inactive.

periodate gave **9**; decarboxylation of **9** gave 1-methyl-2-pyrrolidinone [specific activity 137,900 dpm/mmol (97.6%)] and CO_2 [specific activity 650 dpm/mmol (0.46%)].

On the basis of the experiments with **1**-*2*-^{14}C and **7**-*2*-^{14}C, it is evident that the major pathway of the periodate oxidation of 1-methyl-2,3-piperidinedione (**1**) is *via* intermediates which maintain integrity of the label. Furthermore, a second and minor pathway of formation for the observed product is also present; that is, **1** in the absence of oxidant is capable of conversion to an intermediate in which the label is scrambled. The formation of the symmetrical cyclopropanedione **28** would satisfy this requirement.

According to the postulated mechanism of the periodate oxidation of α-ketoacyl derivatives as shown in Scheme II, the cyclopropanone **27** is irreversibly converted to the cyclopropanedione **28**. No experimental evidence has been presented yet to rule out a possible equilibrium between **27** and **28**. The existence of such an equilibrium or of one among **27**, **27a**, and **27b** would

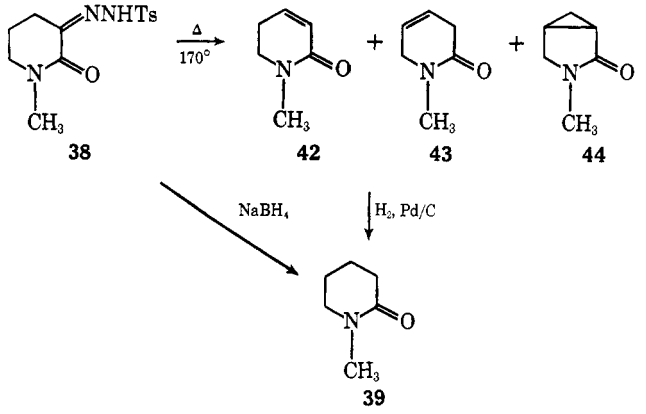


27 **27a** **27b**

readily explain the observed scrambling in **9**. Such equilibria would eliminate the necessity for postulating the ketene derivative **30**. However, the existence of any equilibrium between **27** and **28** or **27a** and **27b** has been excluded by degradation of the 1-methyl-2,3-piperidinedione-*2*-^{14}C recovered from the pH 9 solution after 50 hr.

The degradation of 1-methyl-2,3-piperidinedione is shown in Schemes III and IV. The dione **1** was con-

Scheme IV



38 **42** **43** **44** **39**

verted to its tosylhydrazone **38** and sodium borohydride reduction of **38** gave 1-methyl-2-piperidinone (**39**) in 14% yield. Alternatively, pyrolysis of the tosylhydrazone **38** gave a mixture of the three lactams **42**, **43**, and the 1-oxo-2-methyl-2-azabicyclo[3.1.0]hexane (**44**), the latter probably being formed by insertion of the carbene intermediate formed from **38** and comprising about 30% of the lactam mixture. Hydrogenation of this mixture gave the piperidinone **39** and the unchanged cyclopropyl derivative **44**, readily separated by gc. Hydrolysis of **39** followed by reductive methylation gave a 76% yield of 5-dimethylaminopentanoic acid (**40**) after isolation by ion exchange chromatography and sublimation. Conversion to the phenyl ketone **41** *via* the intermediate acid chloride and oxidation of **41** with chromium trioxide gave benzoic acid (**36**) and 4-dimethylaminobutanoic acid (**34**) in 63 and 54% yield, respectively.

This procedure was now applied to 1-methyl-2,3-piperidinedione-*2*-^{14}C (**1**) which had been allowed to stand in an aqueous pH 9 buffer for 50 hr in each of two separate experiments. If equilibration had occurred between **27** and **28** or **27a** and **27b** both carbonyl carbons of **1** would have been labeled in the recovered material. However, degradation gave benzoic acid [specific activity 5050 dpm/mmol (97.6%)] and 4-dimethylaminobutanoic acid [specific activity 7 dpm/mmol (0.1%)] demonstrating the retention of label in the amide carbonyl. In a second experiment, benzoic acid [specific activity 10,600 dpm/mmol (97.7%)] and 4-dimethylaminobutanoic acid [specific activity 43 dpm/mmol (0.4%)] were obtained. Clearly, essentially no scrambling had occurred and all of the activity of **1** had remained at C-2.

The finding that no scrambling occurred in the 1-methyl-2,3-piperidinedione-*2*-^{14}C (**1**) after reisolation from pH 9 solution, but that it does occur in the 3-carboxy-1-methyl-2-pyrrolidone (**9**) subsequently isolated if periodate is added requires two pathways of formation for the latter. One must involve intermediates derived from **1** in which the labeling pattern becomes scrambled on standing at pH 9 followed by oxidation. For this we postulate the sequence through the cyclopropanedione **28**.[22] However, the entire reaction cannot proceed through this path since such a course would require equivalence of label at the amide and carboxyl carbons of **9** as a result of symmetry in both the cyclopropanedione **28** and hydroxycyclopropenone anion **30**. The other path must be the major route and proceeds with retention of labeling integrity *via* the direct oxidation of cyclopropanone **28** to 3-carboxy-1-methyl-2-pyrrolidinone (**9**). Under normal conditions, that is without prior aging at pH 9, this latter path predominates to the extent of about 99%.

Experimental Section[23]

1-Methyl-2,3-piperidinedione (1). A. By Periodate Oxidation of Glycol 7. To a solution of 837 ml of H_2O, 93 ml of 0.10 *N* HCl, and 150 mmol (32.10 g) of sodium periodate was added 25 mmol

(22) Attempts to trap and isolate the postulated cyclopropanedione intermediates have so far failed.

(23) Solvent evaporations were carried out *in vacuo* using a Berkeley rotary evaporator. All melting points are uncorrected. Infrared (ir) spectra were measured in Nujol for solids and as thin films for liquids on a Perkin-Elmer 137 spectrophotometer and are given in cm^{-1}. Ultraviolet (uv) spectra were recorded on a Cary Model 14 instrument and maxima in 95% ethanol are reported in nanometers. Nuclear magnetic resonance (nmr) spectra were obtained in $CDCl_3$ (unless otherwise noted) with either a Varian A-60 or T-60 spectrometer; peak positions are given as δ values downfield from tetramethylsilane as internal standard, except that sodium trimethylsilylpropanesulfonate was used as internal standard in aqueous solutions. Mass spectra were obtained on a Varian Associates M-66 instrument and high-resolution mass spectra were obtained on a CEC 21-110B spectrometer. Mass peaks are reported at 70 eV followed by relative intensities. All radioactive counting was performed on a Nuclear Chicago Corporation Mark I liquid scintillation computer (Model 6880); all counts are in disintegrations per minute (dpm) relative to an external standard and are corrected for background. Counting times were such that all counts are accurate to ± 1% or less of the values reported. $BaCO_3$ was assayed for radioactivity by the method of Woeller.[24] Gas chromatography was performed on a 30% QF-1 on Chromosorb P column, 10 ft × $^1/_4$

(4.0 g) of 3-hydroxy-3-hydroxymethyl-*N*-methyl-2-piperidone (**7**). The solution was stirred at room temperature in the dark for 10 hr, 200 g of ice was added followed by sufficient sodium bisulfite to destroy excess oxidant, the pH was adjusted to 8 with potassium carbonate, and the resulting solution was continuously extracted with methylene chloride for 83 hr. Evaporation of the methylene chloride, addition of 50 ml of benzene, and reevaporation gave 2.62 g (82.5%) of crystalline **1**. Recrystallization from ether–petroleum ether (30–60°) gave α-ketoamide **1**: mp 79–82°; ir 1660 (amide C=O), 1720 (C=O); uv 259; nmr 3.50 (t, 2 H), 3.03 (s, 3 H), 2.67 (t, 2 H), 2.15 (m, 2 H); mass spectrum *m/e* 127 (15, M^+), 100 (98), 99 (100), 98 (80).

Anal. Calcd for $C_6H_9NO_2$: C, 56.7; H, 7.1; N, 11.0. Found: C, 56.7; H, 7.0; N, 11.1.

B. By Ozonolysis of Olefin 5. At −78° and an ozone flow rate of 0.08 mmol/min, a solution of 40 mmol (5.01 g) of 1-methyl-3-methylene-2-piperidone (**5**) in 100 ml of absolute ethanol was ozonized until approximately 40 mmol of ozone had been consumed. Dimethyl sulfide (10 ml) was added, the reaction mixture was allowed to stand under nitrogen at −78° overnight, excess dimethyl sulfide and solvent were evaporated at room temperature, and the residue was dissolved in benzene. The benzene solution was chromatographed on silica gel and eluted with benzene, benzene–ether (1:1), ether, ether–acetone (1:1), and acetone to give 3.30 g (66%) of **1**. Recrystallization from ether–petroleum ether gave material identical with **1** prepared above from glycol **7**.

3-Carboxy-1-methyl-2-pyrrolidinone (9). A. By Periodate Oxidation of Glycol 7. General Procedure. 3-Hydroxy-3-hydroxymethyl-1-methyl-2-piperidone (**7**) (10 mmol, 1.60 g) was added rapidly to 500 ml of water containing 10.0 g of $Na_2B_4O_7 \cdot 10H_2O$ and 60 mmol (12.70 g) of sodium periodate. Stirring at room temperature in the dark for 16 hr was followed by addition of sodium bisulfite to destroy excess periodate. The solution was adjusted to pH 8 with $NaHCO_3$, continuously extracted with methylene chloride for 48 hr, 6 *N* hydrochloric acid was added to pH 1, and the solution was continuously extracted with methylene chloride for 72 hr. Evaporation of the methylene chloride gave 1.15 g (80%) of **9**. Recrystallization from ethyl acetate or acetone–hexane gave 3-carboxyl-1-methyl-2-pyrrolidinone (**9**): mp 92–94°; uv 197; ir 1670, 1760, 2500–3000; nmr 11.27 (s, 1 H), 3.45 (m, 3 H), 2.90 (s, 3 H), 2.41 (m, 2 H); mass spectrum *m/e* 143 (100, M^+), 99 (84), 98 (96).

Anal. Calcd for $C_6H_9NO_3$: C, 50.3; H, 6.3; N, 9.8. Found: C, 50.3; H, 6.5; N, 10.0.

B. By Periodate Oxidation of 1-Methyl-2,3-piperidinedione (1). 1-Methyl-2,3-piperidinedione (**1**) (1.68 g, 13.5 mmol) was oxidized with periodate by the general procedure and evaporation of the final methyl chloride extract gave 880 mg (45%) of 3-carboxy-1-methyl-2-pyrrolidinone (**9**) identical with material prepared above.

C. By Hydrolysis of 3-Ethoxycarbonyl-1-methyl-2-pyrrolidinone (11). 3-Ethoxycarbonyl-1-methyl-2-pyrrolidinone (**11**),[11] 2.0 g, and 50 ml of 6 *N* NaOH were stirred at 60° for 8 hr, the pH was adjusted to 8, and the solution was extracted with methylene chloride (three 50-ml portions). The aqueous solution was then acidified to pH 1 and continuously extracted with methylene chloride for 24 hr. After evaporation of methylene chloride there remained 1.0 g (60%) of the acid **9**.

Decarboxylation of 3-carboxy-1-methyl-2-pyrrolidinone (9) was effected by heating 143 mg (1 mmol) at 150° until carbon dioxide evolution ceased. The 1-methyl-2-pyrrolidinone (**10**) formed was identical with an authentic sample by gc, nmr, and ir.

1-Methyl-3-methylene-2-piperidone (5). A mixture of 30 mmol (4.28 g) of 1-methylnipecotic acid (**4**) and 25 ml of acetic anhydride was refluxed for 3 hr after which the flask was cooled in ice–water, the contents were added to a cold, aqueous solution of K_2CO_3 (100 g in 200 ml of H_2O), and the mixture was stirred at 0° for 4 hr. Additional carbonate was added until the solution was at pH 8 and the aqueous solution was extracted continuously with methylene chloride for 48 hr. The methylene chloride was evaporated to give 3.48 g (93%) of **5**: nmr 6.16 (m, 1 H), 5.21 (m, 1 H), 3.36 (t, 2 H), 3.00 (s, 3 H), 2.58 (t, 2 H), 1.87 (m, 2 H); uv 209; ir 890, 1610, 3040, 1650; mass spectrum *m/e* 125 (100 M^+), 124 (62), 97 (12); gc (8 ft × $^3/_8$ in.; 175°; 120 ml/min); R_t 10.0 min.

Anal. Calcd for $C_7H_{11}NO$: C, 67.2; H, 8.9; N, 11.2. Found: C, 66.9; H, 8.9; N, 11.1.

3-Epoxymethylene-1-methyl-2-piperidone (6). A solution of 30 mmol (3.75 g) of 1-methyl-3-methylene-2-piperidone (**5**) and 60 mmol (10.30 g) of *m*-chloroperbenzoic acid in 60 ml of methylene chloride was stirred at room temperature for 21 hr. After transferral to a separatory funnel and addition of 300 ml of methylene chloride, a saturated aqueous solution containing 3 mol of $NaHSO_3$ was slowly added to decompose excess peracid. Washing with saturated $NaHCO_3$ solution removed the *m*-chlorobenzoic acid and evaporation of the methylene chloride gave 3.72 g (88%) of **6**: mass spectrum *m/e* 141 (97, M^+), 140 (100), 135 (60), 112 (100), 98 (28); ir 1250, 3050, 1660; uv 201; nmr 3.42 (t, 2 H), 3.11 (d, 1 H, J = 7 Hz), 2.88 (s, 3 H), 2.60 (d, 1 H, J = 7 Hz), 1.94 (m, 4 H).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.6; H, 7.9; N, 9.9. Found: C, 59.5; H, 7.6; N, 9.4.

3-Hydroxy-3-hydroxymethyl-1-methyl-2-piperidone (7). A solution of 24 mmol (3.38 g) of 3-epoxymethylene-1-methyl-2-piperidone (**6**) in 120 ml of 6% perchloric acid was stirred at room temperature for 16 hr after which the pH was taken to 8 with solid sodium bicarbonate and the solution was extracted continuously with methylene chloride for 2 days. Removal of the solvent gave **7** in quantitative yield as a viscous liquid which solidified upon standing: ir 1650, 3450; mass spectrum *m/e* 159 (0.2, M^+), 141 (2), 128 (16), 125 (100); nmr (D_2O) 3.66 (s, 1 H), 3.60 (s, 1 H), 3.37 (t, 2 H), 2.90 (s, 3 H), 1.93 (m, 4 H).

Acetonide of 3-Hydroxy-3-hydroxymethyl-1-methyl-2-piperidone (8). A mixture of 520 mg (3.26 mmol) of 3-hydroxy-3-hydroxymethyl-1-methyl-2-piperidone (**7**), 70 ml of acetone, 100 ml of petroleum ether (30–60°), and 50 mg of *p*-toluenesulfonic acid monohydrate was boiled with azeotropic removal of water for 45 hr. One gram of Na_2CO_3 was added, the petroleum ether and acetone were evaporated, the residue was dissolved in 10 ml of water, and the aqueous solution was extracted with methylene chloride (six 20-ml portions). Evaporation of the methylene chloride gave a quantitative yield of the acetonide **8** which was distilled at 100° (1.5 mm): mass spectrum *m/e* 199 (13, M^+), 184 (48), 141 (100), 127 (35), 112 (13); ir 1670; nmr 4.39 (d, 1 H, J = 8 Hz), 3.79 (d, 1 H, J = 8 Hz), 3.32 (t, 2 H), 2.91 (s, 3 H), 1.95 (m, 4 H), 1.47 (s, 3 H), 1.42 (s, 3 H).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.6; N, 7.0. Found: C, 60.1; H, 8.9; N, 7.2.

Phenylhydrazone of 1-Methyl-2,3-piperidinedione (12). A. *Via* **Phenyldiazonium Chloride.** A solution of phenyldiazonium chloride prepared from 18.4 g (200 mmol) of aniline was added to an ice-cold solution of 3-carboxy-1-methyl-2-piperidone (31.5 g), 400 ml of water, and potassium hydroxide (12 g). After being stirred for 5 min, the solution was brought to pH 3.5 with glacial acetic acid and kept at 0° for 48 hr. The precipitate was removed, washed with water until the washings were neutral, and dried *in vacuo* at 40° to give 34.0 g (82%) of **12**, mp 186–188° after recrystallization from aqueous ethanol: nmr (CD_3OD) 7.27 (m, 5 H), 3.31 (t, 2 H), 2.98 (s, 3 H), 2.52 (t, 2 H), 1.93 (m, 2 H).

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.6; H, 7.0; N, 19.3. Found: C, 66.6; H, 7.2; N, 19.3.

B. From the Ozonolysis Product of 5. Ozonolysis of 1-methyl-3-methylene-2-piperidone (**5**) as above and addition of trimethyl phosphite followed by a phenylhydrazine solution (9.0 g of sodium acetate and 5.0 g of phenylhydrazine hydrochloride in 50 ml of water) led to immediate precipitation of **12**, identical with the product prepared in A, above.

The same phenylhydrazone **12** of 1-methyl-2,3-piperidinedione (**1**) resulted by addition of phenylhydrazine to the solution obtained by treating the glycol **7** with 75 mol % of sodium periodate.

3-Carboxy-1-methyl-2-piperidone (13). A solution of 113 g (1 mol) of 1-methyl-2-piperidone, 2.2 l. of benzene, and 500 g of diethyl carbonate was refluxed for 15 hr with azeotropic removal of water after which 150 g (3.5 mol) of a dispersion of NaH in mineral oil was added to the benzene solution at room temperature. Heating at reflux for 9 hr was followed by cooling to room temperature, slow addition of 900 ml of 4 *N* HCl, and separation and evaporation of the organic layer. The residue was dissolved in water, the two aqueous solutions were combined, the pH was adjusted to 8 with sodium bicarbonate, and the solution was continuously extracted with methylene chloride for 72 hr. The aqueous solution was then adjusted to pH 1 with concentrated hydrochloric acid and continuously extracted for 72 hr with methylene chloride. Removal of the solvent followed by crystallization of the residue from ethyl acetate gave 63.0 g (40%) of **13**: mp 115–120° dec (lit.[25] mp 119°).

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in., unless otherwise specified. All elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

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Anal. Calcd for $C_7H_{11}NO_3$: C, 53.5; H, 7.1; N, 8.9. Found: C, 53.6; H, 7.1; N, 9.1.

***N,N*-Dimethyl-2-oxobutanamide (14).** Thionyl chloride, 18 g, was added to 10.2 g (100 mmol) of 2-oxobutanoic acid in 20 ml of methylene chloride, the mixture was heated at reflux for 4 hr and then cooled to −78°, and 20.0 g of dimethylamine was added. The mixture was allowed to warm to room temperature and 50 ml of water was added. The pH was first taken to 1 with 10% HCl and then to 8 with saturated sodium bicarbonate solution after which it was continuously extracted with methylene chloride for 72 hr. Removal of the solvent gave 9.9 g of liquid which was fractionally distilled giving 3.65 g (28%) of **14**: bp 67–70° (5 mm); ir 1650, 1720 (C=O); nmr (neat) 2.93 (s, 6 H), 2.75 (q, 2 H), 1.10 (t, 3 H); gc (130°, 150 ml/min) R_t 28.6 min.

Anal. Calcd for $C_6H_{11}NO_2$: C, 55.8; H, 8.6; N, 10.9. Found: C, 55.9; H, 8.8; N, 11.2.

***N,N*-Dimethylmethylmalonamic Acid (15). A. By Periodate Oxidation of *N,N*-Dimethyl-2-oxobutanamide (14).** *N,N*-Dimethyl-2-oxobutanamide (**14**), 1.09 g (8.5 mmol), was oxidized at pH 9 with sodium periodate according to the general procedure. Removal of the methylene chloride gave 850 mg (69%) of **15** as a viscous liquid. Chromatography on silica gel, eluting with 30% acetone in methylene chloride, gave 340 mg (28%) of product, which was recrystallized from ethyl acetate–cyclohexane: mp 74–76°; ir 1630, 1740; nmr 10.93 (s, 1 H), 3.72 (q, 1 H), 3.14 (s, 3 H), 2.99 (s, 3 H), 1.41 (d, 3 H), mass spectrum *m/e* 145 (70, M^+), 101 (55), 100 (100).

Anal. Calcd for $C_6H_{11}NO_3$: C, 49.6; H, 7.6; N, 9.6. Found: C, 49.6; H, 7.5; N, 9.5.

B. By Hydrolysis of Ethyl *N,N*-Dimethylmethylmalonamate (16). Ethyl *N,N*-dimethylmethylmalonamate was hydrolyzed with excess 2 *N* NaOH at room temperature for 15 hr after which the pH was adjusted to 1 with 10% hydrochloric acid, the solution was continuously extracted for 48 hr with methylene chloride, and the organic solvent was evaporated giving 2.90 g (100%) of a crystalline residue, mp 74–76°, and identical with the acid prepared above after crystallization from ethyl acetate–cyclohexane.

Ethyl *N,N*-Dimethylmethylmalonamate (16). Thionyl chloride, 40 ml, was added to 18.4 g (100 mmol) of potassium ethyl methylmalonate and the mixture was heated at 60° for 3 hr. Excess thionyl chloride was removed, 40 ml of methylene chloride was added, the mixture was cooled to −78°, 25 g of dimethylamine was added slowly, the reaction mixture was allowed to warm to room temperature, the solution was filtered, and the solid was washed with benzene. The combined benzene–methylene chloride solution was washed with 1 *N* HCl (two 60-ml portions) and then with 50 ml of H_2O and the organic phase was evaporated. Fractional distillation of the residue gave 11.4 g (66%) of ethyl *N,N*-dimethylmethylmalonamate (**16**), bp 77° (3 mm); ir and nmr identical with that reported.[12]

2-Oxoheptanamide (18). Thionyl chloride, 15 ml, was added to 15.1 g (105 mmol) of 2-oxoheptanoic acid (**19**) and 110 ml of methylene chloride and the mixture was stirred for 96 hr. Ammonia was bubbled through the solution until the effluent was alkaline and the methylene chloride was then removed and 175 ml of concentrated ammonium hydroxide was added. The precipitate was removed by filtration and chromatographed on silica gel with acetone as the eluting solvent (25-ml fractions). Addition of petroleum ether to fractions 5 and 6 gave a crystalline solid which was sublimed at 80° (20 μ) yielding **18**, mp 106–107° (lit.[26] mp 109°).

2-Oxoheptanoic acid (19) was prepared as described.[27]

Butylmalonamic Acid (20). 2-Oxoheptanamide (**18**) (1 mmol, 143 mg) was oxidized at pH 9 with sodium periodate following the general procedure. After the addition of sodium bisulfite to remove excess oxidant, the aqueous solution was saturated with sodium chloride and continuously extracted with methylene chloride for 5 days. Evaporation of the methylene chloride and addition of 10 ml of petroleum ether gave a precipitate which was sublimed at 90° (10 μ) to give 30 mg (19%) of butylmalonamic acid (**20**): mp 129–131° dec; ir 1650, 1680, 1740; nmr (acetone-d_6) 6.5–7.4 (br s, 2 H), 3.28 (t, 1 H), 1.90 (m, 2 H), 1.36 (m, 4 H), 0.87 (t, 3 H).

Anal. Calcd for $C_7H_{13}NO_3$: C, 52.8; H, 8.2; N, 8.8. Found: C, 53.0; H, 8.3; N, 8.9.

Periodate Oxidation of Ethyl 2-Oxobutanoate (21). Preparation of Methyl Ethyl Methylmalonate (24) and Methyl Ethyl Methylhydroxymalonate (24). Ethyl 2-oxobutanoate (**21**)[28] (1.48 g, 11.4 mmol) was oxidized at pH 7 with periodate according to the general procedure. Excess ethereal diazomethane was added to the residue after evaporating the methylene chloride extract of the acidic solution, and after standing at room temperature for 3 hr, the solvent was evaporated. Gas chromatography of a 1% aliquot (89°, 150 ml/min) showed the presence of three components.

Fraction 1, R_t 1.9 min, was methyl propionate.

Fraction 2, R_t 23.7 min, was characterized as methyl ethyl methylmalonate (**23**), and was present to the extent of 10%: nmr 4.19 (q, 2 H), 3.71 (s, 3 H), 3.43 (q, 1 H), 1.41 (d, 3 H), 1.24 (t, 3 H).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.5; H, 7.6. Found: C, 52.3; H, 7.6.

Fraction 3, R_t 58.6 min, was characterized as methyl ethyl methylhydroxymalonate (**24**) and was present to the extent of 17%: ir 1750, 3600; nmr 4.24 (q, 2 H), 3.75 (s, CH_3, superimposed on br s, 4 H), 1.62 (s, 3 H), 1.27 (t, 3 H).

Anal. Calcd for $C_7H_{12}O_5$: C, 47.7; H, 6.8. Found: C, 47.6; H, 6.9.

Methyl Ethyl Methylmalonate (23). Potassium ethyl methylmalonate, 18.4 g, and 40 ml of thionyl chloride were heated at 60° for 3 hr, excess thionyl chloride was evaporated, and 20 ml of methanol was added to the residue. After standing at room temperature for 10 min, the reaction mixture was added to 400 ml of half-saturated sodium bicarbonate, the aqueous solution was extracted with methylene chloride (four 80-ml portions), the methylene chloride was dried and evaporated, and the residue was distilled giving methyl ethyl methylmalonate as the fraction boiling at 61–63° (4.5 mm).

***tert*-Butyl 2-Oxobutanoate (22).** To a 50-ml high-pressure tube immersed in Dry Ice–acetone were added 3.0 ml of ether, 0.5 ml of concentrated sulfuric acid, 14 ml of isobutylene, and 9.9 g of 2-oxobutanoic acid, and the sealed tube was shaken at room temperature for 25 hr. The tube was then cooled and the contents added to 60 ml of ice–water, 25 ml of ether, and enough sodium bicarbonate to neutralize the sulfuric acid. The aqueous layer was extracted with four additional 10-ml portions of ether and the combined extracts were dried and evaporated giving 11.74 g (76%) of *tert*-butyl ester **22**, bp 55–60° (6–7 mm).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.8; H, 8.9.

Periodate Oxidation of *tert*-Butyl 2-Oxobutanoate (22). *tert*-Butyl Hydrogen Methylmalonate (25). *tert*-Butyl 2-oxobutanoate (**22**) (1.80 g, 11.4 mmol) was oxidized at pH 9 with periodate following the general procedure. Evaporation of the combined extracts of the pH 8 solution yielded 420 mg of starting α-keto ester. The aqueous layer was acidified to pH 4 with 1 *M* phosphoric acid and extracted continuously for 2 days with methylene chloride which was dried, and evaporated leaving 1.03 g (67%) of *tert*-butyl hydrogen methylmalonate (**25**), purified by short-path distillation, bp (bath temperature) 75° (0.02–0.03 mm).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.2; H, 8.1. Found: C, 55.0; H, 8.2.

2-Methylaminoethylmalonic Acid (32). 3-Ethoxycarbonyl-1-methyl-2-pyrrolidinone (5.13 g) and 70 ml of 9 *N* NaOH were heated at 70° for 21 hr. One-third of the above hydrolysate was removed and added to 100 ml of water, the solution was saturated with carbon dioxide, partially evaporated to remove the ethanol, and the residue was dissolved in 370 ml of water, after which 5.10 g of *p*-bromobenzenesulfonyl chloride was added and the mixture stirred at room temperature for 24 hr. Acidification gave 3.00 g (79%) of the *o*-bromosulfonyl derivative of **32**, mp 128–129° after crystallization from chloroform.

Anal. Calcd for $C_{12}H_{14}BrNO_6S$: C, 37.9; H, 3.7; N, 3.7; S, 8.4. Found: C, 37.8; H, 3.8; N, 3.7; S, 8.4.

4-Dimethylaminobutanoic Acid Hydrochloride (34). 1-Methyl-2-pyrrolidinone, 20 mmol, 1.98 g, 12 ml of water, and 3.2 g of sodium hydroxide were heated at reflux for 10 hr, the solution was adjusted to pH 8 with 10% hydrochloric acid, 8 ml of 36% formaldehyde and 1.0 g of 10% Pd/C were added, and the mixture was shaken under hydrogen for 16 hr. The solution was filtered, the filtrate at pH 8 was applied to an anion exchange column (500 ml of resin, OH^- form, AG-1X-8), and, after washing the column until neutral, the product was eluted with 2 *N* HCl, collecting the first 800 ml of acidic eluate. The solvent was evaporated and the residue was sublimed at 130° (50 μ), giving 2.80 g of 4-dimethylaminobutanoic acid hydrochloride (**34**), mp 150–152° (lit.[29] mp 145–147°).

Anal. Calcd for $C_6H_{14}ClNO_2$: C, 43.0; H, 8.4; Cl, 21.2; N, 8.4. Found: C, 43.0; H, 8.3; Cl, 21.0; N, 8.4.

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γ-Dimethylaminobutyrophenone (35). 4-Dimethylaminobutanoic acid hydrochloride, 4.5 mmol (750 mg), and 10 ml of thionyl chloride were warmed at 60° for 1 hr. Excess thionyl chloride was removed *in vacuo* and 30 mmol (4.0 g) of aluminum chloride was added followed by 10 ml of benzene. The reaction mixture was stirred at room temperature for 3 hr, poured onto 100 g of ice–water containing 10 ml of 10% HCl, the benzene layer was separated, and the aqueous phase was adjusted to pH 11 with 10% sodium hydroxide. It was then extracted with methylene chloride (seven 30-ml portions) which was dried and evaporated leaving a residue of 840 mg (98%) of the clear liquid ketone. An analytical sample was prepared by gas chromatography (178°, 100 ml/min), R_t 38.4 min (lit.[30] bp 139–141° (5 mm)).

Anal. Calcd for $C_{12}H_{16}NO$: C, 75.4; H, 9.0; N, 7.3. Found: C, 75.4; H, 9.1; N, 7.5.

Chromic Acid Oxidation of γ-Dimethylaminobutyrophenone (35). To 840 mg (4.4 mmol) of γ-dimethylaminobutyrophenone were added 10 ml of trifluoroacetic acid and 1 ml of concentrated sulfuric acid, then a solution of 36 ml of acetic acid, 5 ml of water, and 2.25 g (22.5 mmol) of chromium trioxide was added dropwise over 2 hr. The reaction mixture was warmed at 50–60° for 2 hr, the solvent was evaporated, the residue was dissolved in 100 ml of 5% sulfuric acid, and 10 g of sodium metasulfite was added to destroy excess oxidant. Extraction with methylene chloride (six 25-ml portions) which was then dried and evaporated give 350 mg (65%) of benzoic acid (**36**) after sublimation.

The aqueous solution was adjusted to pH 10 with 10% sodium hydroxide, the chromium hydroxide was removed by filtration, and the filtrate was adjusted to pH 4 with 10% hydrochloric acid and applied to 500 ml of cation exchange resin (AG-50W-X8, hydrogen ion form, 200–400 mesh). After washing with water until neutral, the product was eluted with 2 *N* ammonium hydroxide and the first 700 ml of alkaline eluate was collected. Evaporation until pH 8 was obtained was followed by application to 300 ml of anion exchange resin (AG-1X-8, OH^- form, 200–400 mesh). The column was washed until neutral, the product was eluted with 2 *N* hydrochloric acid, the acidic solution was evaporated, and the residual solid was sublimed at 130° (20 μ) to give 426 mg (63%) of *N*,*N*-dimethyl-β-alanine hydrochloride (**37**), mp 183–186° (lit.[31] 180–182°), after crystallization from isopropyl alcohol.

1-Methyl-2,3-piperidinedione Tosylhydrazone (38). A solution of 1.86 g (10 mmol) of *p*-toluenesulfonyl hydrazide dissolved in 30 ml of acetic acid and 50 ml of water was added to 570 mg (4.5 mmol) of 1-methyl-2,3-piperidinedione. The solution was stirred at room temperature for 24 hr and filtered, and the precipitate was recrystallized from aqueous ethanol giving 975 mg (73%) of the tosylhydrazone **38**: mp 154–164° dec; nmr ($CDCl_3$·TFA) 7.80 (m, 2 H), 7.38 (m, 2 H), 3.71 (t, 2 H), 3.38 (s, 3 H), 2.68 (t, 2 H), 2.46 (s, 3 H), 2.18 (m, 2 H).

Anal. Calcd for $C_{13}H_{17}N_3O_3S$: C, 52.9; H, 5.8; N, 14.2; S, 10.8. Found: C, 52.7; H, 5.7; N, 14.4; S, 10.7.

Preparation of 1-Methyl-2-piperidone (39). A. By Borohydride Reduction of the Tosylhydrazone 38. A mixture of 590 mg (2 mmol) of 1-methyl-2,3-piperidinedione tosylhydrazone (**38**), 1.14 g (30 mmol) of sodium borohydride, and 35 ml of THF was heated at reflux for 20 hr and then slowly added to 50 ml of 10% hydrochloric acid. The THF was removed, the pH was adjusted to 8 with potassium carbonate, and the solution was continuously extracted with methylene chloride for 6 days. Evaporation of solvent and gas chromatography of the residue gave 31 mg (14% yield) of 1-methyl-2-piperidone (**39**), R_t 73.9 min (164°, 50 ml/min).

B. By Pyrolysis of 1-Methyl-2,3-piperidinedione Tosylhydrazone (38). With the system at aspirator pressure, 1.05 g (3.56 mmol) of the tosylhydrazone **38** was heated at 170–180° until evolution of nitrogen ceased. The residue, 360 mg of a yellowish liquid, was gas chromatographed on 10% KOH, 10% polybutylene glycol on 60–80 firebrick (5 ft × 1/4 in.; 130°; 100 ml/min) giving a major peak at R_t 5.7 min which was a mixture of **42**, **43**, and **44** in 25% yield: mass spectrum *m/e* 111 (M^+), 82, 68; uv 248; nmr signals at 0.65, 1.10, 1.78, 2.34, 2.71, 2.93, 2.96, 3.38, 3.86, 5.70, 5.90, 6.47.

This mixture of **42**, **43**, and **44** was dissolved in 50 ml of ethyl acetate, 50 mg of 10% Pd/C was added, and it was hydrogenated at 43 psi. After hydrogen consumption ceased, the catalyst was removed and the filtrate was evaporated. Gas chromatography of the residue on 10% SE-30 on Chromosorb W (20 ft × 1/4 in.; 140°; 100 ml/min) gave two peaks, R_t 26.9 and 29.0 min, in a 1:2.5 ratio, respectively.

The material R_t 26.9 min was characterized as the cyclopropyl derivative **44**: ir 1675; mass spectrum *m/e* 111 (100, M^+), 82 (34), 68 (20); nmr 3.35 (m, 2 H), 2.73 (s, 3 H), 1.78 (m, 2 H), 1.10 (m, 1 H), 0.65 (m, 1 H).

The material R_t 29.0 min was characterized as 1-methyl-2-piperidone (**39**), isolated in an overall 9% yield and identical with an authentic sample.

5-Dimethylaminopentanoic Acid Hydrochloride (40). The same procedure was used for preparing **40** from 1-methyl-2-piperidone (**39**) as was previously used for preparing 4-dimethylaminobutanoic acid hydrochloride (**34**). Sublimation at 140° (10 μ) gave **40** in 76% yield: mp 164–166° (lit.[32] mp 163–165°).

δ-Dimethylaminovalerophenone (41) was synthesized in 85% yield from 5-dimethylaminopentanoic acid hydrochloride (**41**) in the same manner as previously reported for the preparation of γ-dimethylaminobutyrophenone (**35**): nmr 7.85 (m, 2 H), 7.35 (m, 3 H), 2.88 (t, 2 H), 2.20 (t, 2 H), 2.10 (s, 6 H), 1.70 (m, 4 H); gc (183°, 150 ml/min), R_t 21.9 min.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.1; H, 9.3; N, 6.8. Found: C, 76.0; H, 9.4; N, 6.7.

Chromic acid oxidation of dimethylaminovalerophenone (41) was carried out as previously described for γ-dimethylaminobutyrophenone (**35**). Benzoic acid (**36**) and 4-dimethylaminobutanoic acid (**34**) were obtained in 65 and 54% yields, respectively.

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