furnished **14** as a yellow oil: bp 196–198° (0.6 mmHg) (12.25 g, 57%); λ_{max} 258 mμ (log ε 3.90); $\mu_{C=O}$ 1735 cm^{-1}; δ 1.70–3.10 (m, six protons), 3.61 (s, CH_3N), 3.66, 3.78, 3.83 (s, three OCH_3), 7.08 (s, pyrrole ring proton).

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.52; H, 6.24; N, 4.42.

Dimethyl 2-Phenyl-4-oxo-4,5,6,7-tetrahydroindole-3,5-dicarboxylate (15). To a suspension of sodium hydride (57% dispersion in mineral oil, 2.1 g, 0.05 mol, washed with pentane to remove the mineral oil) in distilled THF (50 ml) containing 0.2 ml of methanol, a solution of **13** (6.85 g, 0.019 mol) in distilled THF (25 ml) was added in dropwise portions over a 30-min period. The reaction mixture throughout this addition was kept under a nitrogen atmosphere and was stirred while the mixture was heated to reflux. Upon completion of the addition of **13**, the mixture was refluxed for an additional 3 hr, then cooled to 5° and acidified with acetic acid (20 ml) and water (200 ml). The aqueous mixture was extracted with chloroform (2 × 100 ml), and the combined organic extract was washed with brine (200 ml), dried (Na_2SO_4), and evaporated to dryness in vacuo. The brown tarry residue (6.05 g) was then chromatographed on a silica gel column (1000 g) and elution with 20% ethyl acetate–80% benzene furnished a brown semisolid (2.23 g) which was recrystallized from benzene–ether to give **15** as a colorless powder (0.93 g, 15%): mp 121–123°; μ_{NH} 3440 and 3300, $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 2.10–3.10 (m, four protons), 3.45 (t, CH, J = 6 Hz), 3.65 and 3.68 (s, two OCH_3), 7.30–7.50 (m, phenyl protons), 10.13 (broad s, NH).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28. Found: C, 66.11; H, 5.15; N, 4.25.

Dimethyl 1-Methyl-4-oxo-4,5,6,7-tetrahydroindole-3,5-dicarboxylate (16). Following the procedure described for the synthesis of **15**, reaction of **14** (4.5 g, 0.015 mol) with sodium hydride (57% dispersion, 2.1 g, 0.05 mol) in distilled THF (50 ml) containing 0.2 ml of methanol furnished a dark orange oil (5.20 g) which was chromatographed on a silica gel column (500 g). Elution of the column with 5% ethanol–95% benzene afforded **16** as a tan solid (1.85 g, 46%): mp 95–100°; $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 2.30–3.00 (m, four protons), 3.50 (t, CH, J = 7.5 Hz), 3.56 (s, CH_3N), 3.71 and 3.78 (s, two OCH_3), 7.23 (s, indole ring proton).

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.95; H, 5.85; N, 4.88.

Acknowledgment. The author wishes to thank Ms. Mary Anne Oram for technical assistance, Mr. Michael Scaros for carrying out the catalytic hydrogenation reactions, and the Searle Laboratories column chromatography group.

Registry No.—**1a**, 147-85-3; **16**, 535-75-1; **2a**, 54384-27-9; **2b**, 54383-97-0; **2b** dicyclohexylamine salt, 54383-98-1; **4a**, 54383-99-2; **4b**, 54384-00-8; **5a**, 54384-01-9; **5b**, 54384-02-0; **8a**, 56-40-6; **8b**, 56-41-7; **8c**, 69-91-0; **8d**, 107-97-1; **9a**, 1738-76-7; **9b**, 42854-62-6; **9c**, 54384-04-2; **9d**, 54384-06-4; **10a**, 54384-07-5; **10b**, 54384-28-0; **10c**, 54384-08-6; **10d**, 54384-09-7; **11a**, 54384-10-0; **11b**, 54384-29-1; **11c**, 54384-11-1; **11d**, 54384-12-2; **12**, 54384-13-3; **13**, 54384-14-4; **14**, 54384-15-5; **15**, 54384-16-6; **16**, 54384-17-7; methyl (4-chloroformyl)butyrate, 1501-26-4; dicyclohexylamine, 101-83-7; dimethyl acetylenedicarboxylate, 762-42-5; *p*-toluenesulfonic acid, 104-15-4; benzyl alcohol, 100-51-6.

References and Notes

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Rearrangement of Pyruvates to Malonates. Synthesis of β-Lactams

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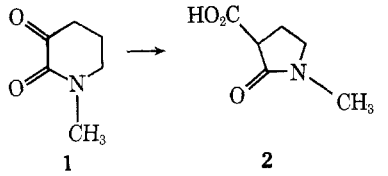
The oxidative rearrangement of α-ketoacyl derivatives to malonates has been extended to include a synthesis of β-lactams by oxidative (periodate) ring contraction of α-keto-γ-lactams. The rearrangement introduces a carboxyl group at the α carbon of the β-lactam and is capable of converting β-substituted α-keto-γ-lactams to the α,α-disubstituted ring-contracted derivatives. The application of the reaction to several simple mono- and bicyclic lactams is presented.

The fortuitous observation that periodate treatment of the δ-lactam 1-methyl-3-hydroxy-3-hydroxymethyl-2-piperidinone led to the formation of γ-lactam **2** was followed by the determination that the actual precursor of **2** was the α-keto-δ-lactam **1**.[1] The possibility that related acyclic derivatives might undergo a similar rearrangement was realized with the demonstration that α-keto esters and amides can be rearranged to malonates.[1] Rearrangement of the δ-lactam **1** to the ring-contracted derivative **2** also suggested



1 **2**

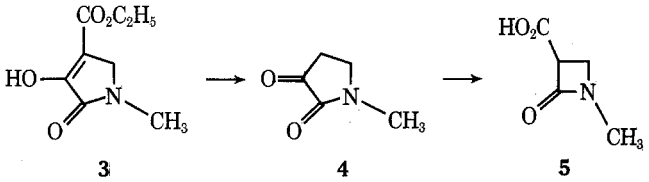
the possibility of extending the reaction to provide a synthesis of β-lactams. Formation of β-lactams by this ring-contraction reaction represents a potential synthesis of β-lactams containing either mono- or difunctionality at the α carbon, and the rearrangement conditions of periodate at room temperature and neutral pH suggested compatibility of the approach with the presence of a variety of substituents.

Examination of the numerous methods currently available for β-lactam synthesis[2] reveals that nearly all approaches require ring closure directly to the four-membered ring. Of the few methods utilizing ring expansion or ring contraction,[3] only the photolytic Wolff rearrangement of 3-diazo-2,4-pyrrolidinediones appears to have received more than passing attention.[3d,e] The potential advantages of β-lactam formation by ring contraction under mild and

selective conditions prompted the synthesis of several model compounds, and we now report application of the oxidative rearrangement to the monocyclic α-keto-γ-lactam 4 and to the bicyclic derivatives 14, 15, and 16.[4]

Results and Discussion

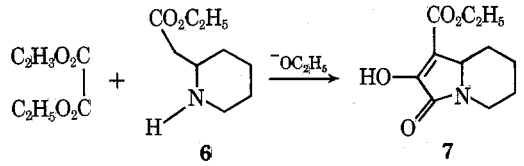
The first γ-lactam examined was 1-methyl-2,3-pyrrolidinedione (4), which is the γ-lactam most analogous to the δ-lactam 1. An unsuccessful attempt has been reported[5a] to obtain 4 from the 4-ethoxycarbonyl derivative 3 by chloroform extraction after hydrolysis in hydrochloric acid, and subsequently the isolation of 4 as its 4-benzylidine derivative was reported.[10] Using the reaction conditions employed previously but with isolation by continuous extraction followed by sublimation, we have obtained 4 in 63% yield.



3 4 5

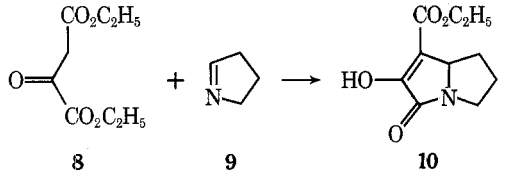
The oxidation of 4 with sodium periodate in an aqueous buffer at pH 7.0 was carried out in the manner used for oxidation of the δ-lactam 1. The resulting carboxy-β-lactam 5 was obtained in 30% yield, without any attempt at optimization. We then turned from this monocyclic example to examine bicyclic models which would be analogous with the β-lactam antibiotics.

Preparation of Azabicyclo[4.3.0]nonane-8,9-diones. The required precursor of a β-lactam which can lead to a simple bicyclic analog of the cephalosporin antibiotics is the α-keto-γ-lactam 14. In turn, 14 could be obtained from the bicyclic ester 7 in the same manner used for the conversion of 3 to 4. Two approaches have been applied successfully to the synthesis of bicyclic esters such as 7. One approach, an extension of the method used to synthesize the monocycle, is illustrated by the synthesis of 7 from the β-amino ester 6 and diethyl oxalate.[11] The other approach is



6 7

an extension of the imine-addition method,[6a] illustrated by the synthesis of 10 from 1-pyrroline (9) and diethyl oxalacetate (8).[12] Although 10 has also been obtained by condensation of ethyl 2-pyrrolidinylacetate with diethyl oxalate,[11] the synthesis of 7 from 2,3,4,5-tetrahydropyridine (12) has not been reported.

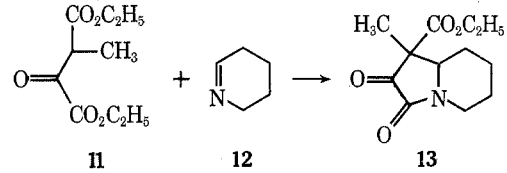


8 9 10

Initially 7 was obtained according to the published procedure.[11] We then planned to make 7-substituted derivatives, e.g., 13, by alkylation of 7 with methyl iodide, but alkylation under a variety of conditions (sodium hydride in tetrahydrofuran or dimethylformamide, thallous ethoxide in benzene) gave exclusively the O-alkylated product. Similar resistance to C-alkylation was apparently encountered and circumvented by condensation of substituted pyruvic acids or oxalacetates with an imine.[8]

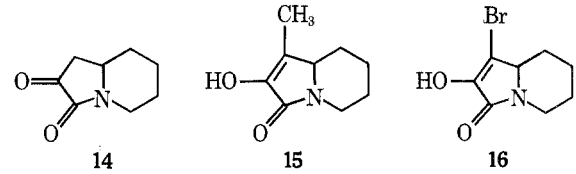
Application of the imine-addition approach to the synthesis of 13 required use of imine 12 (Δ^1-piperideine), which is an elusive species. No attempt was made to isolate it as the monomer. Instead, a solution of 12 in ethanol–ether was prepared by dehydrohalogenation of *N*-chloropiperidine according to the method used for the preparation of 1-pyrroline,[13] which in turn is based on the procedure for the preparation of a trimer of 12, α-tripiperideine.[14] The preparation of *N*-chloropiperidine by treatment of piperidine acetate with hypochlorite was replaced by the more convenient procedure employing direct formation from piperidine with *N*-chlorosuccinimide.[15]

Before attempting the condensation reaction with a substituted ester, we carried out the condensation of 12 with diethyl oxalacetate. Refluxing the ethanol–ether solution of 12 with a benzene solution of diethyl oxalacetate produced the desired ester 7 in 48% yield, thus providing 7 more conveniently than by the published procedure.[11] The analogous condensation of 12 with the substituted ester 11 required a longer reaction time and produced 13 in 30% yield.



11 12 13

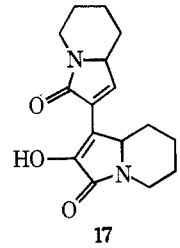
Acid-catalyzed hydrolysis and decarboxylation of ethyl ester 7 was carried out in refluxing 10% hydrochloric acid, resulting in a 60% yield of 14. A similar procedure applied to 13 gave 15 in 74% yield. The bromo analog 16 was obtained in 80% yield from 14 by bromination at room temperature either in a heterogeneous mixture with copper(II) bromide in methylene chloride or by homogeneous bromination with copper(II) bromide in methanol.



14 15 16

The properties of these bicyclic analogs of 2,3-pyrrolidinediones parallel the properties of the monocyclic compounds. The infrared spectra of 4, 13, and 14 all show ketone absorptions between 1767 and 1783 cm^{-1} and amide absorptions between 1700 and 1720 cm^{-1}. In contrast, 15 exhibits a broad band at 1662 cm^{-1} and 16 gives a similar band at 1680 cm^{-1}. Neither 4 nor 14 give a positive test with ferric chloride, whereas the ethyl ester 7 and the enols 15 and 16 display deep colors of burgundy or indigo.

The similarity of 14 with its monocyclic analogs is further illustrated by its self-condensation to 17, a conversion



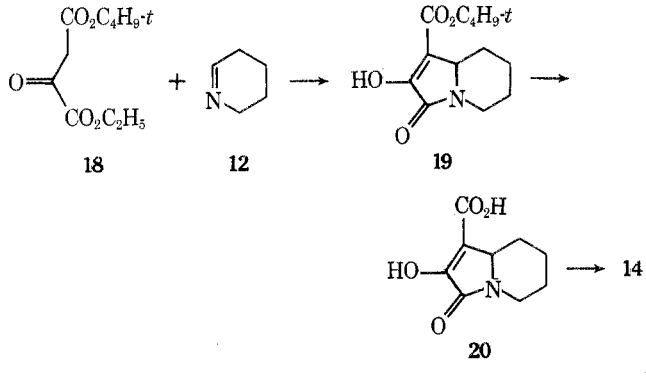
17

sufficiently facile to preclude chromatography on silica gel or storage (even at 0°) for more than several days. Infrared and ultraviolet absorption data are consistent with an enolized structure, and the NMR spectrum confirms the indicated structure by exhibiting a vinyl doublet at δ 6.6 and two sharp singlets for the enolic proton at δ 12.9. The simi-

lar aldol condensation products from monocyclic lactams[5a] are reported to produce a green to green-blue color with ferric chloride; **17** gives a green color.

2,3-Pyrrolidinediones with no substituents at C-4 invariably appear to be obtained from 4-alkoxycarbonyl precursors,[5] and the conversion of these precursors to the C-4 unsubstituted derivatives is usually quite troublesome. Our own experience with the conversion of the ethyl ester **7** to the C-7 unsubstituted derivative **14** has indicated that the time required for complete conversion is also sufficient to allow for significant side reactions. Numerous variations in the procedure resulted in no improvement in yield. Basic hydrolysis to an acid such as **20**, generally expected to be easy, has repeatedly proved to be impossible,[8,16,17] as was the case with **7**. However, if the acid could be obtained by a nonhydrolytic procedure, then decarboxylation could perhaps be achieved under conditions milder than those required for hydrolysis of the ester.

Accordingly, we prepared such 7-carboxyl derivatives from their *tert*-butyl esters, and these acids were found to decarboxylate readily at room temperature in the presence of kieselgel or powdered glass. Application of these observations to an improved synthesis of **14** required the acid **20**, which was obtained conveniently and quantitatively from the *tert*-butyl ester **19** by treatment with acetic acid saturated with HBr. The *tert*-butyl ester **19** was obtained from **12** in the same manner used for the synthesis of ethyl ester **7**. Condensation of the ester **18**[18] with **12** gave **19** in 60% yield.



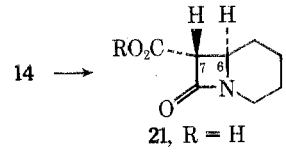
18 12 19 20

The acid **20** decarboxylated with such ease that only spectral characterization was possible. A dilute aqueous sample of **20** prepared for ultraviolet characterization decarboxylated rapidly at room temperature, giving a uv absorbance corresponding exactly with the absorbance of **14**.

Preparative decarboxylation of **20** can be carried out under a variety of conditions. Shaking **20** as a solution in methanol–acetone and a small amount of acetic acid in the presence of powdered Pyrex leads to decarboxylation at room temperature within ~2 hr. Decarboxylation in refluxing methanol–acetone is complete after about 1 hr, whereas the same conditions in the presence of powdered Pyrex lead to total decarboxylation in less than 7 min. Progress of the conversion can be followed in the uv, and the uv spectra of these solutions indicate the complete absence of **17**, the product of self-condensation. The conversion of **19** to **14** thus is quantitative, and sublimation results in a 90% yield of **14**, the residue being a mixture of **14** and **17** as seen from its infrared spectrum.

Periodate Oxidation of Bicyclic α-Ketolactams 14, 15, and 16. The rate of oxidation of **14** was determined conveniently by monitoring the uv absorbance of periodate at 223 nm. A constant value corresponding to uptake of approximately 100 mol % of periodate was obtained within 15–20 min. Comparable rates of periodate uptake were observed during the oxidation of the bicyclic analogs **15** and **16**. Phosphate buffers with sodium as the cation were used initially, but the heterogeneous reaction mixtures which frequently resulted frustrated attempts to follow the oxidation. Buffering solutions prepared by titrating phosphoric acid with lithium hydroxide proved satisfactory, but are limited by extensive precipitation above pH ~7.7.

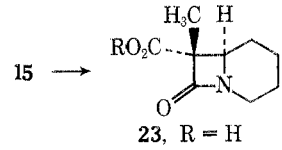
Oxidation of **14** proceeded smoothly to give **21**[19] in 70% yield. Neither the 60- nor the 100-MHz NMR spectra of **21**,



21, R = H
22, R = CH_3

or its methyl ester **22**, in deuteriochloroform revealed H-7 resolved from other downfield absorptions. However, use of pyridine instead of chloroform gave rise to substantial differential effects on the chemical shifts of the downfield protons, and a 220-MHz spectrum completely resolved H-7 from the other two absorptions. The 1.8-Hz coupling constant establishes the C-6 and C-7 protons as trans;[20] no absorption corresponding to the cis isomer was observed. Samples of ester **22** were obtained from both crude and recrystallized **21** and subjected to gas chromatographic conditions which successfully resolved esters **27** and **28**.[21] Both samples gave a single symmetrical peak, indicating the absence of the cis isomer.

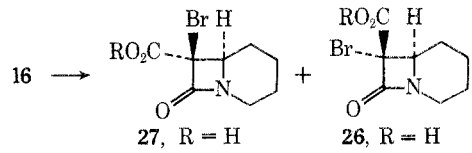
Methyl analog **15** was chosen as a simple example for determining the effect on ring contraction of an alkyl substituent at the β carbon of an α-keto-γ-lactam. Oxidation of **15** produced in 50% yield only one of the two possible β-lactam isomers, **23**, which was subsequently shown by X-ray



23, R = H
24, R = CH_3

crystallography[22] to have the carboxyl group located trans to the fused ring. The crude oxidation product was esterified and chromatographed[21] in the same manner as the unsubstituted β-lactam **21**. No peak corresponding to the other isomer was observed.

The bromo analog **16** was viewed as a potential intermediate for the synthesis of other α-keto-γ-lactams and as a compound which could give a β-lactam amenable to a variety of synthetic manipulations. Oxidation of **16** led to a 40% yield of β-lactam, subsequently shown to be a mixture of the stereoisomers **25** and **26**. Gas chromatography[21] of the



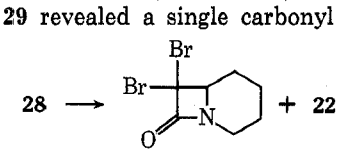
27, R = H **26**, R = H
25, R = CH_3 **28**, R = CH_3

product obtained by esterification with diazomethane gave two peaks which corresponded in molecular formula with the desired methyl ester. The ratio of peak areas was approximately 9:1. Complete separation of the isomers was then achieved by column chromatography on kieselgel, and the isomer ratio determined from gas chromatography was confirmed.

The separated isomers were hydrolyzed in nearly quantitative yield to the acids **25** and **26** with 1 equiv of potassi-

um hydroxide in 50% aqueous dioxane. X-Ray crystallographic studies[22] of these acids indicated that the carboxyl group of the major isomer, **25**, is located in the same manner as the carboxyl group of **21** and **23**, that is, trans to the fused ring.

Neither the NMR spectrum nor TLC of the original 9:1 mixture of esters **27** and **28** indicated the presence of other materials, but gas chromatography of the mixture led to several peaks in addition to those corresponding to **27** and **28**. The minor ester **28** initially was isolated by gas chromatography of mixtures enriched in this isomer, and these enriched mixtures gave relatively much greater amounts of the other materials. It was then found that stepwise lowering of the injection port temperature increased the peak area due to **28** at the expense of the combined peak areas due to the other materials; peak area due to **27** always remained the same. Injection of pure **27** gave a single peak; injection of pure **28** gave the peak corresponding to **28** plus previously observed peaks, thus indicating that these contaminating materials are due to decomposition of **28**, but not **27**, in the metal injection port of the gas chromatograph. The decomposition products were collected and gave R_f values on TLC distinctly different from the values for either **27** or **28**, confirming that they were not present initially but were formed during gas chromatography. The structures of the two major decomposition products were established as **22** and the α,α-dibromo-β-lactam **29**. The ir spectrum of **29** revealed a single carbonyl absorption at



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1782 cm^{-1}, and the NMR spectrum retained all of the absorptions characteristic of these bicyclic β-lactams.

Further studies of the scope of the oxidative ring contraction reaction of α-keto-γ-lactams are continuing and will be the subject of a subsequent report.

Experimental Section[23]

1-Methyl-2,3-pyrrolidinedione (4).[24] 4-Ethoxycarbonyl-3-hydroxy-1-methyl-2-oxo-3-pyrroline (**3**, 10.0 g, 0.054 mol)[5a] was heated for 50 min in refluxing 2.9 *M* HCl (500 ml). Continuous extraction with CH_2Cl_2 for 48 hr gave, after evaporation of solvent, a brown solid which was purified by sublimation at 90° (10 μ) to give 3.88 g (63%) of off-white solid: ir (film) 1767, 1701 cm^{-1}; NMR δ 2.75 (2 H, t, *J* = 5.5 Hz), 3.13 (3 H, s), 3.74 (2 H, t, *J* = 5.5 Hz). Alternatively, the crude solid was recrystallized from ether, giving **4** with spectral properties (ir, NMR) identical with the above, mp 89–91°.

Anal. Calcd for $C_5H_7NO_2$: C, 53.1; H, 6.2; N, 12.4. Found: C, 52.8; H, 6.0; N, 12.3.

7-Ethoxycarbonyl-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (7) from 2,3,4,5-Tetrahydropyridine (12). Ethyl sodioethoxalylacetate (52.5 g, 0.25 mol) was stirred with a mixture of water (125 ml), benzene (250 ml), and 6 *N* H_2SO_4 (42 ml). The benzene layer was separated, washed with water (2 × 150 ml), and dried (Na_2SO_4). An ether–ethanol solution of **12** was prepared from piperidine (21.5 g, 0.25 mol)[13] and the solutions of **12** and diethyl oxalacetate were combined and refluxed for 3 hr, then washed with brine (2 × 50 ml), dried (Na_2SO_4), and evaporated. The remaining dark oil was dissolved in 30 ml of ether. On standing, crystals were formed in 48% yield. Spectral (ir and NMR) properties and the melting point (115–116°) were identical with those of an authentic sample.[11]

7-Ethoxycarbonyl-7-methyl-8,9-dioxo-1-azabicyclo[4.3.0]-nonane (13). Diethyl methyloxalacetate (**11**, 12.8 g, 0.063 mol)[25] was dissolved in benzene (125 ml) and refluxed for 18 hr with a solution of **12** prepared from piperidine (0.125 mol) as described previously. The solution was washed with brine (2 × 50 ml) and dried (Na_2SO_4) and the solvents were evaporated. The remaining dark oil was dissolved in ether)~20 ml) and allowed to stand overnight, giving crystals in 30% yield. Recrystallization from hexane–$CHCl_3$ gave colorless prisms: mp 92–93°; ir 1777, 1727 cm^{-1} (br); NMR δ 0.9–2.2 (6 H, m), 1.23 (3 H, t, *J* = 7 Hz), 1.4 and 1.5 (3 H, two singlets), 2.93 (1 H, m), 3.3–4.6 (2 H, m), 4.17 (2 H, q, *J* = 7 Hz); mass spectrum *m/e* (rel intensity) 239 (M^+, 11), 211 (10), 166 (100).

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.2; H, 7.2; N, 5.9. Found: C, 60.1; H, 7.0; N, 6.0.

7-*tert*-Butoxycarbonyl-8-hydroxy-9-oxo-1-azabicyclo-[4.3.0]non-7-ene (19). A mixture of piperidine (2.72 g, 0.032 mol), *N*-chlorosuccinimide (7.45 g, 0.56 mol), and ether (165 ml) was stirred at room temperature for 0.5 hr and filtered, and the precipitate was rinsed with ether (10 ml). The filtrate was washed with water (4 × 100 ml) and brine (50 ml) and then dried ($MgSO_4$). Just before use in the next step the extract was filtered and concentrated to about 20 ml.

The ether solution of *N*-chloropiperidine was added over a period of 7 min to a stirred solution of absolute ethanol (16 ml) containing 85% KOH (2.11 g, 0.032 mol of KOH). The internal temperature of the ethanol solution was kept between 5 and 10° during addition. After addition was complete the cooling bath was replaced with a large water bath at room temperature and the ethanol–ether mixture was stirred in this bath for 2 hr. After filtration of the mixture and rinsing of the precipitate with absolute ethanol, a filtrate with a volume of 32 ml was obtained.

To 30 ml of the above solution was added freshly distilled ethyl 3-*tert*-butoxycarbonyl-2-oxopropionate[18] (3.24 g, 0.015 mol) in benzene (15 ml). The resulting solution was refluxed for 3.5 hr, then allowed to stand overnight at room temperature. With the internal temperature of the reaction mixture <25°, 2.9 *M* HCl was added until the aqueous layer gave pH ~1. The mixture was then diluted with water (50 ml) and extracted with benzene (2 × 100 ml). The combined extracts were washed with brine (30 ml), dried ($MgSO_4$), filtered, and evaporated to give a yellow solid which was chromatographed on silica gel (40 g) with $CHCl_3$. Recrystallization from $CHCl_3$–hexane gave after collection of three crops 2.28 g (60%) of colorless crystals: mp 142–146°; ir 1701 (s), 1675 (s), 1631 cm^{-1} (m); NMR δ 0.7–2.2 (5 H, m), 1.58 (9 H, s), 2.2–3.2 (2 H, m), 3.92 (1 H, dd, *J* = 11, 4 Hz), 4.35 (1 H, br dd, $J_{\alpha,kb}$ mgr = 13 Hz), 9.2 (1 H, broad hump); uv (95% EtOH) λ_{max} 245 nm (ε 8820), 304 (5500); uv (H_2O, pH 4.6) 247 (9500), 304 (4250); uv (H_2O, pH 6.0) 240 (6850), 304 (10,300); mass spectrum *m/e* (rel intensity) 253 (M^+, 1), 197 (3), 180 (7), 153 (18), 152 (14), 124 (6), 123 (5), 59 (100).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.6; H, 7.6; N, 5.5. Found: C, 61.8; H, 7.6; N, 5.9.

8,9-Dioxo-1-azabicyclo[4.3.0]nonane (14). Ester **7** (300 mg, 1.33 mmol) was heated for 2.5 hr in refluxing 2.9 *M* HCl (15 ml). Continuous extraction with CH_2Cl_2 gave, after drying ($MgSO_4$) and evaporation of solvent, a crude solid which was purified by sublimation at 57° (20 μ) to give 124 mg (60%) of solid: mp 62–66°; ir 1783, 1708 cm^{-1}; nmr δ 1.1–2.3 (6 H, m) 2.4–3.2 (2 H, m), 2.92 (1 H, m), 3.80 (1 H, m), 4.35 (1 H, br dd, $J_{\alpha,\beta}$ = 13 Hz); uv (water, acidic or neutral) λ_{max} 256 nm (ε 4000); mass spectrum *m/e* (rel intensity) 153 (M^+, 85), 125 (66), 41 (100).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.7; H, 7.2; N, 9.1. Found: C, 62.7; H, 7.1; N, 9.3.

7-Carboxy-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (20). To the *tert*-butyl ester **19** (146 mg, 0.58 mmol) in acetic acid (0.7 ml) was added acetic acid saturated with HBr (11.5 ml). After being stirred at room temperature for 10 min the solution was evaporated at room temperature, resulting in a solid which was redissolved without heating in methanol. Evaporation of this solution gave 113 mg (100%) of solid: mp 142–144° dec; ir (Nujol mull) 1661 cm^{-1} (broad); NMR (DMSO-d_6) δ 0.7–2.0 (5 H, m), 2.2–3.2 (2 H, m), 3.7–4.3 (2 H, m); uv (H_2O, pH 6.3) λ_{max} 245 nm (ε 7700), shoulder at ~295 (3200); mass spectrum *m/e* (rel intensity) no observable M^+, 153 (M^+ − 44, 72), 125 (26), 124 (40), 41 (100).

Decarboxylation of Acid 20. Powdered Pyrex was prepared by taking granular Pyrex of minimum 80 mesh and grinding it with mortar and pestle. The amount of glass initially used was arbitrary, but relative amounts were always the same and taken from the same batch.

A. Decarboxylation at Room Temperature. The acid **20** (13 mg, 0.07 mmol) was dissolved in methanol (1.6 ml) and acetone (1.6 ml). After addition of 2 drops of acetic acid and 0.22 g of powdered Pyrex the mixture was shaken on a mechanical shaker at room temperature. Aliquots were periodically removed and their uv spectra indicated the presence only of **14** within 1.5–3.5 hr.

B. Decarboxylation at Reflux and Isolation of 14 by Sublimation. The *tert*-butyl ester **19** (166 mg, 0.65 mmol) was converted to the acid **20** as described previously. After **20** was dissolved at

room temperature in methanol (16 ml) and acetone (16 ml), powdered Pyrex (2.15 g) was added and the stirred mixture was refluxed for 7 min. Examination of the uv spectrum of an aliquot indicated the presence only of **14**. The mixture was cooled to room temperature, filtered through Celite, and evaporated at room temperature to give a residue which was immediately taken up in CH_2Cl_2 (50 ml) and dried ($MgSO_4$) for ca. 15 min. After filtration through Celite and evaporation of solvent, the residue was transferred with CH_2Cl_2 to a sublimer, evaporated, and sublimed at a bath temperature of 57° (10 μ), yielding 89 mg (90%) of **14** identical with authentic material by ir and melting point comparison. An ir spectrum of the residue after sublimation (7 mg) indicated an approximately 1:1 mixture of **14** and **17**.

Aldol Condensation Product from 14 (17). A sample of crude **14** was allowed to stand overnight at room temperature and closed to the atmosphere. Warming the solid to 70° did not result in melting. Recrystallization from hexane–$CHCl_3$ gave a cream-colored, amorphous solid: mp 219–224° dec; ir 1690, 1649, 1580 cm^{-1}; NMR δ 0.9–2.5 (12 H, m), 2.90 (2 H, m), 3.7–4.5 (4 H, m), 6.59 (1 H, d, J = 2 Hz), 12.80 (0.2 H, s), 12.93 (0.8 H, s); uv (95% C_2H_5OH) 249 nm (ϵ 12,300), 297 (14,200); mass spectrum m/e (rel intensity) 288 (M^+, 77), 270 (89), 242 (25), 214 (11), 41 (100).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.6; H, 7.0; N, 9.7. Found: C, 66.6; H, 6.9; N, 9.7.

7-Methyl-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (15). Ester **13** (1 g, 4.2 mmol) was heated for 1.5 hr in refluxing 2.9 M HCl (47 ml). Continuous extraction with CH_2Cl_2 gave, after drying ($MgSO_4$) and evaporation of solvent, a yellow solid which was recrystallized from benzene as prisms (520 mg, 74%): mp 191–193°; ir 3548 (shoulder), 3207 (br), 1662 cm^{-1} (br); NMR δ 0.7–2.4 (6 H, m), 1.85 (3 H, s), 2.82 (1 H, m), 3.50 (1 H, dd, J = 11, 4 Hz), 4.23 (1 H, br dd, $J_{\alpha,\beta}$ = 13 Hz), 8.5 (1 H, broad s); mass spectrum m/e (rel intensity) 167 (M^+, 100), 152 (94).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.6; H, 7.8; N, 8.4. Found: C, 64.6; H, 7.9; N, 8.5.

7-Bromo-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (16). Ketone **14** (1.2 g, 7.8 mmol) copper(II) bromide (3.50 g, 15.7 mmol, pulverized) and CH_2Cl_2 (109 ml) were mechanically stirred in the dark for 22 hr. After filtration through Celite and evaporation of solvent the residue was chromatographed on silica gel (20 g) with $CHCl_3$, giving 1.46 g (80%) of solid which was recrystallized from hexane–$CHCl_3$: mp 121–122° dec; ir 3451 (shoulder), 3078 (br), 1680 cm^{-1}; NMR δ 0.9–2.5 (6 H, m), 2.87 (1 H, m), 3.78 (1 H, dd, J = 11, 4 Hz), 4.29 (1 H, br dd, J = 13 Hz), 9.25 (1 H, s); mass spectrum m/e (rel intensity) 233, 231 (M^+, 33), 152 (100), 124 (37).

Anal. Calcd for $C_8H_{10}BrNO_2$: C, 41.4; H, 4.3; N, 6.0. Found: C, 41.6; H, 4.3; N, 6.1.

3-Carboxy-1-methyl-2-azetidinone (5).[24] A mixture of the pyrrolidinedione **4** (452 mg, 4.0 mmol), sodium periodate (5.14 g, 24.0 mmol), and a sodium–phosphate buffer (0.2 M, 150 ml) of pH 7.0 (before addition of periodate) was stirred in the dark for 24 hr. With ice-bath cooling, the periodate was destroyed by slow addition of aqueous $NaHSO_3$ (2 M, 60 ml) while keeping the pH near 7 by addition of saturated K_2CO_3 solution. The resulting pH 7 solution was reduced to ca. half volume by lyophilization, adjusted to pH 4 with phosphoric acid, and continuously extracted with CH_2Cl_2 for 7 days. The resulting light amber oil (220 mg) was chromatographed on silica gel (15 g) with $CHCl_3$–CH_3OH–HCO_2H (10:1:0.05), yielding 153 mg (30%) of colorless oil: ir (neat) 1745 cm^{-1} (br); NMR δ 2.86 (3 H, s), 3.50 (2 H, m), 4.10 (1 H, m), 9.2 (1 H, s); mass spectrum m/e (rel intensity) 129 (M^+, 15), 101 (100), 84 (10), 73 (30), 72 (21), 58 (37), 55 (80).

Anal. Calcd for $C_5H_7NO_3$: C, 46.5; H, 5.5; N, 10.9. Found: C, 46.3; H, 5.6; N, 10.9.

Oxidation with Sodium Periodate. General Procedure. A 0.2 M buffer was prepared by titrating phosphoric acid with aqueous LiOH. A volume of buffer was chosen such that the concentration of starting material was 0.02 M, sodium periodate was added, and the pH was adjusted to the desired value. Depending on its rate of solution in water, starting material was added all at once as a fine powder, or was added with vigorous stirring over a period of several minutes as a solution (volume ~5% of volume of buffer) in CH_3OH or tetrahydrofuran (THF). Aliquots were removed periodically and examined in the uv. Periodate and iodate were destroyed by addition of an approximately stoichiometric amount of $NaHSO_3$ dissolved in a minimum of water while keeping the pH near 7 by the addition of 2 M NaOH. Following extraction of the neutral solution with CH_2Cl_2, the pH was adjusted to 2.0 with phosphoric acid and the solution was continuously extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and evaporated.

7-Carboxy-8-oxo-1-azabicyclo[4.2.0]octane (21). The ketone **14** (3.34 g, 0.022 mol) was oxidized with $NaIO_4$ (0.044 mol) at pH 6.3 as described above to give **21** in 70% yield. The product was recrystallized from hexane–acetone: mp 145–146° dec; ir 1753, 1722 cm^{-1}; NMR δ 1.2–2.3 (6 H, m), 2.81 (1 H, m), 3.5–4.1 (2 H, m), 3.75 (1 H, d, J = 1.8 Hz), 9.2 (1 H, s); mass spectrum m/e (rel intensity) 169 (M^+, 12), 141 (100), 125 (11), 124 (32), 123 (31), 97 (42).

Anal. Calcd for $C_8H_{11}NO_3$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.9; H, 6.8; N, 8.3.

7-Methoxycarbonyl-8-oxo-1-azabicyclo[4.2.0]octane (22). The acid **21** in ether–methanol (5:1, v/v) was treated with excess CH_2N_2 in ether. After destruction of the excess with acetic acid, evaporation of solvents left **15** as an oil; ir 1760, 1730 cm^{-1}; NMR (CCl_4) δ 1.1–2.3 (6 H, m), 2.75 (1 H, m), 3.4–4.0 (2 H, m), 3.55 (1 H, d, J = 1.8 Hz), 3.70 (3 H, s); mass spectrum m/e (rel intensity) 184 (M^+ + 1, 92), 183 (M^+, 31), 156 (100), 155 (82), 124 (89), 97 (55), 96 (47). An analytical sample was prepared by preparative GC.

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.1; N, 7.6. Found: C, 59.0; H, 7.1; N, 7.6.

7-Carboxy-7-methyl-8-oxo-1-azabicyclo[4.2.0]octane (23). The methyl analog **15** (500 mg, 3.0 mmol) was oxidized with sodium periodate (2.60 g, 12.1 mmol) at pH 6.3 as described above. The resulting solid was recrystallized from hexane–acetone, yielding 285 mg (53%) of colorless prisms: mp 179–181°; ir 1743, 1713 cm^{-1}; NMR δ 1.2–2.1 (6 H, m), 1.52 (3 H, s), 2.76 (1 H, m), 3.6–4.0 (m, 2 H), 10.6 (1 H, s); mass spectrum m/e (rel intensity) 183 (M^+, 4), 155 (68), 41 (100).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.1; N, 7.6. Found: C, 59.0; H, 6.8; N, 7.6.

7-Methoxycarbonyl-7-methyl-8-oxo-1-azabicyclo[4.2.0]octane (24). A solution of the acid **23** (50 mg) in THF (15 ml) was treated with excess CH_2N_2 in ether. The solution was stirred for 18 hr and the solvents were evaporated to yield **17** as an oil: ir 1756, 1725 cm^{-1}; NMR δ 1.0–2.0 (6 H, m), 1.45 (3 H, s), 2.85 (1 H, m), 3.6–4.0 (2 H, m), 3.72 (3 H, s); mass spectrum m/e (rel intensity) 197 (M^+, 6), 169 (69), 166 (32), 138 (66), 137 (66), 41 (100). An analytical sample was prepared by preparative GC.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.9; H, 7.7; N, 7.1. Found: C, 60.9; H, 7.6; N, 7.2.

7-Bromo-7-methyoxycarbonyl-8-oxo-1-azabicyclo[4.2.0]octane (27 and 28). The bromo analog **16** (500 mg, 2.15 mmol) was oxidized with $NaIO_4$ (920 mg, 4.3 mmol) as described above to yield 215 mg (40%) of **19** and **20** as a light yellow oil. A solution of this oil in ether was treated with excess CH_2N_2 in ether. After destruction of the excess with acetic acid and evaporation of solvent, the residue was chromatographed on silica gel (10 g) to give the esters **27** and **28** as a colorless oil. A portion of this oil (166 mg) was chromatographed on kieselgel (23 g) with ether–petroleum ether (bp 30–60°) (3:1 v/v). The major isomer (**27**) was eluted first, and mixed portions containing 11 mg were recycled.

27: 139 mg; ir 1776, 1738 cm^{-1}; NMR (CCl_4) δ 1.2–2.1 (6 H, m), 2.85 (1 H, m), 3.5–4.0 (2 H, m), 3.82 (3 H, s); mass spectrum m/e (rel intensity) 263, 261 (M^+, 2), 235, 233 (20), 182 (100), 154 (14).

28: 15 mg; ir 1776, 1749 cm^{-1}; NMR (CCl_4) δ 1.1–2.2 (6 H, m), 2.82 (1 H, m), 3.5–4.0 (2 H, m), 3.82 (3 H, s); mass spectrum m/e (rel intensity) 263, 162 (M^+, 0.07), 235, 233 (1), 203, 201 (0.5), 182 (7), 154 (1.5), 43 (100).

7-Bromo-7-carboxy-8-oxo-1-azabicyclo[4.2.0]octane (25 and 26). Potassium hydroxide in 50% aqueous dioxane (0.10 M, 4.24 ml) was added to a solution of **28** (111 mg, 0.42 mmol) in 50% aqueous dioxane (2.4 ml). After standing for 12 hr, the solution was added to ice water (20 ml) and extracted with CH_2Cl_2 (3 × 15 ml). The combined extracts were dried ($MgSO_4$) and evaporated to yield 6 mg of unreacted **28** (by TLC comparison).

The aqueous solution was buffered to pH 2.0 with $NaH_2PO_4 \cdot H_2O$ (450 mg) and 3.0 M H_3PO_4. Continuous extraction with CH_2Cl_2 gave **26** (94 mg, 95%) as a solid which was recrystallized from hexane–$CHCl_3$ as colorless needles: mp 180–182° dec; ir 1777, 1719 cm^{-1}; NMR ($CDCl_3$, CD_3OD) δ 1.1–2.3 (6 H, m), 2.84 (1 H, m), 3.6–4.1 (2 H, m); mass spectrum m/e (rel intensity) 249, 247 (M^+, 14), 231, 229 (23), 221, 219 (80), 205, 203 (70), 177, 175 (79), 168 (88), 82 (100).

Anal. Calcd for $C_8H_{10}BrNO_3$: C, 38.7; H, 4.1; N, 5.7. Found: C, 39.0; H, 4.1; N, 5.7.

The major isomer, **25**, was obtained similarly and it crystallized both as a hydrate, mp 97° and 119–120°, and as the anhydrous compound: mp 124–126°; ir 1772, 1724 cm^{-1}; NMR ($CDCl_3$, CD_3OD) δ 1.2–2.2 (6 H, m), 2.87 (1 H, m), 3.6–4.1 (2 H, m); mass spectrum m/e (rel intensity) 231, 229 (M^+ − 18, 4), 221, 219 (3), 168 (14), 41 (100).

Anal. Calcd for $C_8H_{10}BrNO_3$: C, 38.7; H, 4.1; N, 5.7. Found: C, 38.8; H, 4.2; N, 5.6.

7,7-Dibromo-8-oxo-1-azabicyclo[4.2.0]octane (29). A mixture of decomposition products (94 mg) collected by preparative GC of the esters **27** and **28** was chromatographed on kieselgel (11 g) with ether–petroleum ether (3:1 v/v), giving **29** (25 mg), intermediate fractions (16 mg) shown by GC to contain **22** to the extent of ~30%, then **22** (35 mg), identical with an authentic sample by ir, NMR comparison, and GC coinjection. **29** was recrystallized from hexane–$CHCl_3$: mp 73–74°; ir 1782 cm^{-1}; NMR (CCl_4) δ 1.2–2.3 (6 H, m), 2.82 (1 H, m), 3.5–4.0 (2 H, m); mass spectrum *m/e* (rel intensity) 285 (M^+, 1.7), 283 (M^+, 3.2), 291 (M^+, 1.7), 257 (<1), 255 (1), 253 (<1), 212 (46), 210 (80), 208 (50), 204, 202 (93), 176, 174 (86), 123 (82), 95 (27), 44 (100).

Anal. Calcd for $C_7H_9Br_2NO$: C, 29.7; H, 3.2; N, 4.9. Found: C, 30.0; H, 3.3; N, 4.9.

Registry No.—**3**, 4450-97-9; **4**, 42599-26-8; **5**, 42599-27-9; **7**, 54409-76-6; **11**, 759-65-9; **12**, 505-18-0; **13**, 42599-33-7; **14**, 35620-54-3; **15**, 54409-78-8; **16**, 54409-79-9; **17**, 42599-30-4; **19**, 54409-80-2; **20**, 54409-81-3; **21**, 42599-31-5; **22**, 53618-26-1; **23**, 40876-98-0; **24**, 54409-85-7; **25**, 54409-86-8; **26**, 54409-87-9; **27**, 42599-40-6; **28**, 42599-41-7; **29**, 42599-42-8; ethyl sodioethoxalylacetate, 54409-82-4; piperidine, 110-89-4; *N*-chlorosuccinimide, 128-09-6; ethyl 3-*tert*-butoxycarbonyl-2-oxopropionate, 54409-83-5.

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(23) Solvent evaporations were carried out in vacuo using a Berkeley rotary evaporator. All melting points are uncorrected. Infrared (ir) spectra were measured in chloroform (unless otherwise indicated) on a Perkin-Elmer 137 or 337 spectrometer; ultraviolet (uv) spectra were measured using a Cary Model 14 spectrometer; and nuclear magnetic resonance (NMR) spectra were taken in $CDCl_3$ (unless otherwise indicated) on a Varian T-60 spectrometer and are reported as δ values relative to Me_4Si (δ 0). NMR line shape abbreviations include: dd, double doublet, br dd, broad double doublet. Mass spectra were obtained on a CEC 103 instrument. All reactions and continuous extractions were carried out in a nitrogen atmosphere. Chromatography was performed on Merck silica gel (70–230 mesh) or Camag kieselgel (>250 mesh) without binder as specified. Kieselgel chromatography was generally carried out in quartz columns using General Electric manganese-activated zinc silicate, Type T-1 (1%, w/w) as a short-wavelength uv indicator. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.
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Fumaric Acid Formation in the Diels–Alder Reaction of 2-Methylfuran and Maleic Acid. A Reexamination[1]

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The exo-cis Diels–Alder adduct of 2-methylfuran and maleic acid in water slowly reverts to maleic acid, 2-methylfuran, endo-cis adduct, and fumaric acid. Fumaric acid formation in this system has previously been cited to support a nonconcerted [2 + 4] cycloaddition. Present kinetic measurements, however, show that fumaric acid is formed in a very minor side reaction. The sum of the rates of cycloaddition between maleic acid and 2-methylfuran and cycloreversion of exo-cis and endo-cis [2 + 4] adducts is at least 1000 times as fast as fumaric acid formation and suggests that the main reaction proceeds by a concerted path. Possible mechanisms of direct isomerization of the maleic acid in equilibrium with adduct have been tested. Other possible mechanisms leading to fumaric acid are discussed.

The retrodiene reaction,[2] exhibited by the exo-cis adduct (I) from maleic acid and 2-methylfuran, has been asserted to be a nonconcerted reaction.[3] Gagnaire et al.[3] reported that in aqueous solution adduct I undergoes cycloreversion to yield fumaric acid along with maleic acid and 2-methylfuran (eq 1). Fumaric acid, along with exo- and endo-cis adducts, were also reported to form if maleic acid and 2-methylfuran were mixed in aqueous solution. If, however, furan or 2,5-dimethylfuran was used instead of 2-methylfuran, no fumaric acid was observed to form from the maleic acid initially present under similar conditions. On this basis the authors concluded that reversion of I to its ad-