Periodate Oxidation of α-Keto γ-Lactams. Enol Oxidation and β-Lactam Formation. Mechanism of Periodate Hydroxylation Reactions

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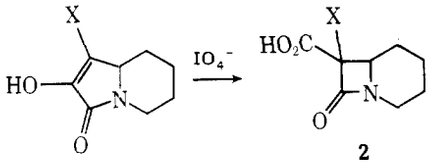
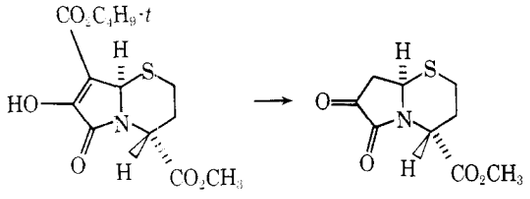
Periodate oxidation of α-keto γ-lactams results in β-lactam formation by oxidative ring contraction and in two modes of enol oxidation. The relative rates of these oxidation paths are related to electron distribution over the three-atom portion comprising the α-keto group and the β carbon, as demonstrated by the dependence of oxidation rate and product distribution on the electronic properties of the β substituent. Depending on the β substituent, some α-keto γ-lactams are also oxidized by iodate. The two modes of enol oxidation and the factors which determine which mode predominates appear to provide a unified mechanistic interpretation for periodate hydroxylation reactions in general.

The formation of β-lactams **2** from α-keto γ-lactams **1** by oxidative ring contraction with periodate has been shown to be compatible with the presence of several substituents, X = H, CH_3, and Br, on the β carbon of **1**,[1] and factors which appear to influence stereochemistry have been discussed.[2]



1 **2**

During investigations of the scope of this reaction with regard to variation of the β-substituent X, a potential precursor of a cephalosporin analogue, γ-lactam **3**, was prepared.[3] Conversion as described previously[1] gave the α-keto lactam **4**, but periodate oxidation of **4** led to no evidence for the presence of a β-lactam.[4]



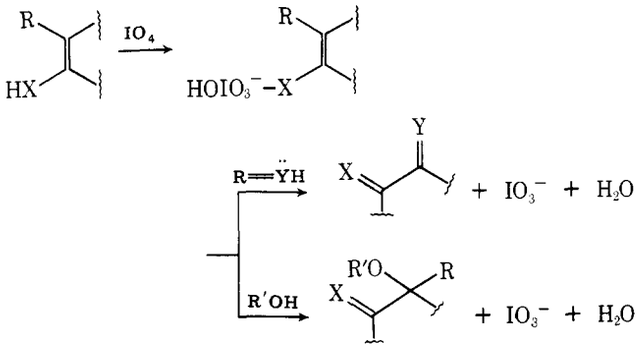
3 **4**

To preclude the possibility of decomposition of products under the acidic isolation conditions, we sought a method for converting acidic materials to neutral species directly in the aqueous medium in which oxidation occurs, thus allowing isolation by rapid extraction while maintaining the pH around neutrality. A procedure which appeared applicable is the esterification of carboxylic acids with triethyloxonium fluoroborate (TEOF) in neutral or slightly alkaline aqueous solution.[5]

During the development of this procedure for isolation of products from the oxidation, bromolactam **5** was oxidized and the reaction solution was treated with TEOF to yield not only the expected β-lactam esters **6**, but also a new product which we have shown to be the oxalyl derivative **7**, the product of enol oxidation of **5**. Also, oxidation of **4** followed by treatment of the reaction solution with TEOF gave only a low yield of β-lactam.[4] This result, along with the apparent preclusion of decomposition of any β-lactams produced, forced a consideration of periodate oxidation reactions which could be competitive with rearrangement. With the establishment of structure **7**, an investigation of enol oxidation of compounds of type **1** was undertaken, the results of which are the subject of this report.

The variety of periodate hydroxylation reactions is large.[6,7] These reactions are usually referred to as active methylene, enol, and non-Malapradian oxidation, or "over-oxidation", or by reference to the entire molecular structure, e.g., oxidation of reductones, phenols, and flavonols. The analogy of the oxidation of the latter compounds to that of simple enols has been pointed out,[6] and a mechanism (Scheme I) for the oxidation of these enolic compounds has been proposed,[8] but a unified mechanistic picture encompassing periodate hydroxylation reactions in general has remained unknown.

Scheme I. Proposed[8] Mechanism for Enol Oxidation by Periodate



The oxalyl products (**10** and **7**) of enol oxidation of enols **1** (X = CH_3 and Br) are readily accommodated by the proposed mechanism, which allows for the possibility that hydroxylic solvent is necessary for oxidation. A consequence of this possibility is that exclusion of hydroxylic solvent could leave oxidative rearrangement as the only remaining reaction. But enol **8** in chloroform solution was unreactive in the presence of tetrabutylammonium periodate, and the addition of methanol, while allowing for oxidation, led to no β-lactam formation and also gave none of the β-methoxy-α-keto γ-lactam **11**, the expected product if oxidation had taken place according to Scheme I. This result suggested the existence of an alternative mechanism for enol oxidation.

It has been noted that monocyclic α-keto γ-lactams analogous to the bicyclic lactams **1** with X = CH_3 and Br (**8** and **5**) display phenolic properties[9] and that the acidity of monocyclic lactams analogous to **1** with X = $CO_2C_2H_5$ (**18**) is comparable to that of carboxylic acids.[10] The similarity in properties of the bicyclic analogues **1** to those of the monocyclic compounds has been amply demonstrated.[1] Whereas the methyl and bromo analogues of **1** gave good yields of β-lactam when oxidized by periodate, the ethoxycarbonyl analogue **18** rapidly consumed more than 100 mol % of periodate with complete exclusion of the ring contraction reaction. This result suggested an inverse relationship between enol oxidation and oxidative rearrangement rates, with both rates depending on enol acidity, this in turn being influenced by the β substituent, X.

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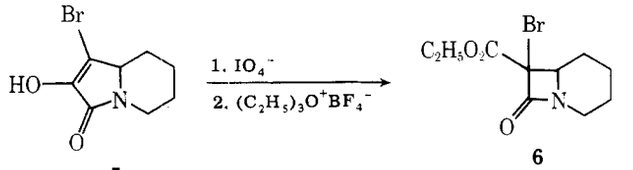
To complete a spectrum of lactams 1 with X having varying electronic properties, the methoxy analogue **15** was prepared. Oxidation of **15** proceeded rapidly, but again with complete exclusion of the rearrangement reaction. Whereas the oxalyl product **16** from the oxidation of **15** is accommodated by the proposed mechanism for enol oxidation[8] (as are the products of enol oxidation of 1 with X = CH_3 and Br), the formyl product **19**, isolated after more thorough examination of the oxidation of ethoxycarbonyl analogue **18**, is not. This result allows for the proposal of two mechanisms by which the enols 1 are oxidized, with the relative rates of these two enol oxidation modes and of oxidative rearrangement depending upon electron distribution over the three-atom enolic system. Having two oxidation modes available for rationalization of enol oxidation also provides for the possibility of developing a unified explanation for periodate hydroxylation reactions.

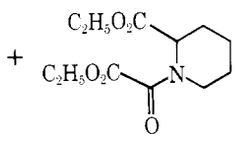
Results

Initial investigations of the scope of the oxidative ring contraction reaction were directed only to the question of whether or not oxidation would produce a β-lactam, and continuous extraction at pH 2 was a reliable method for isolation of the product β-lactam acids. Application of this procedure to isolation of products from the oxidation of bromo analogue **5** gave both cis and trans β-lactam acids, but in only 40% yield.[1] Oxidations at pHs greater or less than 6.3 reduced the yield, and oxidation at pH 5 completely eliminated the rearrangement reaction. A striking but apparently dissimilar dependence of β-lactam yield on pH during oxidation was also observed during oxidation of the unsubstituted keto lactam **21**. β-Lactam yield was reduced to 50% at pH 7 and 25% at pH 8–9, although decreasing the pH to 4 reduced the yield only slightly. At pH 6.3, ethoxycarbonyl analogue **18** consumed >100 mol % of periodate and yielded no β-lactam.

Oxidation of **5** in the usual way, but followed by treatment of the reaction solution with TEOF and extraction at neutral pH, yielded three products: both isomers of β-lactam **6** and a third product, **7**. The mass spectrum of **7** clearly indicated



5 6



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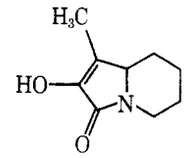
absence of bromine, the NMR spectrum showed multiple ethoxy absorptions, and absorptions consistent with the presence of ester and amide functionalities were present in the IR. These data along with the mass spectral fragmentation pattern and composition data pointed to structure **7**, and it was characterized unambiguously by synthesis from ethyl pipecolate and ethyl oxalyl chloride.

Oxidation of methyl analogue **8** was then reexamined in the light of these results with **5**. Methyl ketone **10** is expected if enol oxidation of **8** takes place similarly to oxidation of **5**, and material with spectral and composition data consistent with structure **10** was indeed isolated. This assignment was confirmed by synthesis of **10** starting with pipecolic acid. It was necessary to block the carboxyl function as its benzyl ester before acylation with ethyl oxalyl chloride. Hydrogenolysis was followed by formation of the imidazolide, and treatment of the latter with the magnesium salt of *tert*-butyl hydrogen



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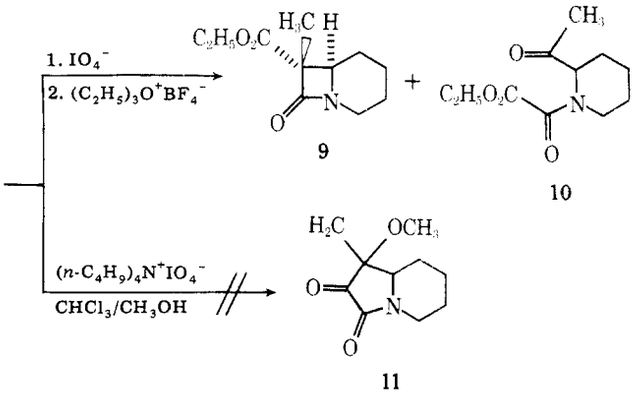
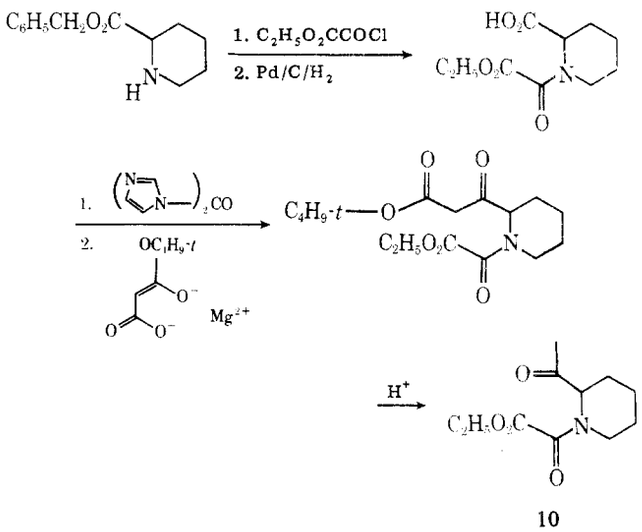


malonate gave the β-keto ester. Cleavage of the *tert*-butyl ester and decarboxylation gave the desired methyl ketone **10**.

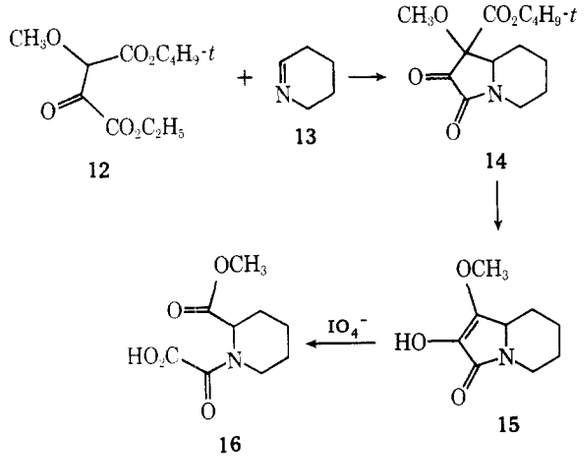


The methyl analogue **8** provided a convenient compound for an examination of the effect of conditions on mode of oxidation. The methyl group NMR absorptions for **8** and for either of the products **9** or **10** are all distinctly different, allowing determination of the oxidation mode by analysis of the crude product. Oxidation of **8** with hydrated periodic acid (H_5IO_6) in tetrahydrofuran (THF) or in aqueous acetic acid stopped after consumption of only 100 mol % of periodate, but the methyl absorptions of crude product corresponded to the presence of a methyl ketone. The phenolic character of **8** and the known reactivity of phenols with iodate suggested invoking enol oxidation by iodate followed by α-hydroxy ketone cleavage by periodate. This invocation remains at least in part equivocal, but it did call attention to the reactivity of enols 1 with iodate, which will be considered later.

The proposed mechanism for enol oxidation (Scheme I)[8] calls for participation of hydroxylic solvent in the reaction, and investigations of the oxidation of flavonols,[11] phenols[12,13] and indoles[14] support this view. On the other hand, the proposed mechanism for oxidative rearrangement[15] does not involve solvent participation. We therefore investigated the oxidation of **8** under anhydrous conditions with tetrabutylammonium periodate in chloroform,[16] determining the concentration of periodate from its UV extinction at 223 nm. (The salt was not isolated since solid tetraethylammonium per-

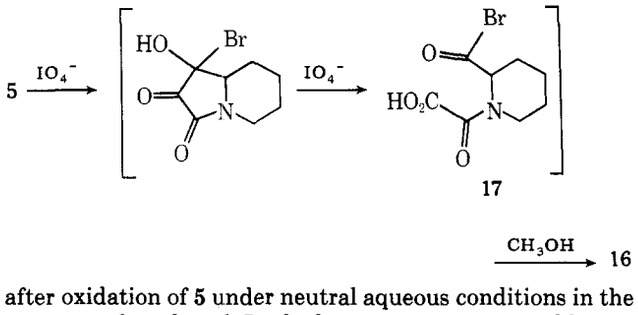
iodate is an explosive substance.[17]) Enol 8 was unreactive under these conditions, there being no consumption of periodate over a 2-h period. Addition of methanol allowed for oxidation,[18] but as was the case with periodic acid in THF or in aqueous acetic acid, only 100 mol % of periodate was consumed, and an IR spectrum of the solution gave absorptions consistent with a product similar to structure **10**. The characteristic β-lactam carbonyl absorption was absent, and absence of the high-frequency ketone absorption expected for the β-disubstituted-α-keto γ-lactam **11** suggested that oxidation had not taken place according to Scheme I. The existence of an alternative mechanism for enol oxidation by periodate was again indicated.

Regardless of the nature of this alternative mechanism, it was necessary to know the effect on ring contraction of an electron-donating group at the β carbon of **1**. We therefore sought the methoxy analogue **15**, which was prepared by the imine-addition approach in a manner analogous to the preparation of methyl analogue **8**.[1] Treatment of *tert*-butyl methoxyacetate with lithium cyclohexylisopropylamide, followed by condensation with diethyl oxalate gave the methoxy-substituted oxalacetate **12** in 60% yield. Condensation of **12** with Δ^1-piperideine (**13**) proceeded rapidly even at 0 °C



to give **14** in 30% yield. Treatment of **14** with acetic acid saturated with HBr led directly to **15**, a crystalline material which was unstable to air. The spectral properties of **14** and **15** are similar to those of previously reported analogues,[1] and the NMR absorption at δ 4.2 for the methoxy group of **15** is noteworthy in that it occurs significantly downfield relative to that observed for aromatic methoxy groups.

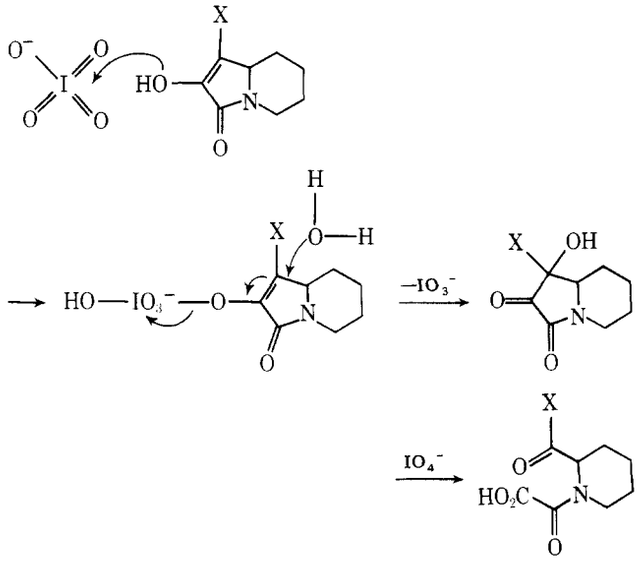
Oxidation of **15** at pH 6.3 with 200 mol % of periodate resulted in complete consumption of periodate within a few minutes and gave glyoxylic acid **16** in 65% yield (based on **14**), isolated by extraction at pH 2 of the sodium chloride saturated reaction solution. No evidence of β-lactam formation was found. Acid **16** was identical with material previously isolated



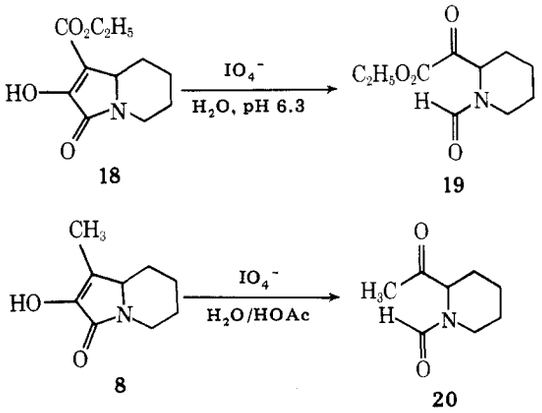
after oxidation of **5** under neutral aqueous conditions in the presence of methanol. In the latter case **16** presumably was formed via the acid bromide **17**, since **5** is unreactive toward methanol, even at reflux.

A pattern in terms of both oxidation rate and product distribution was evident at this point. When oxidized by periodate in neutral aqueous solution, the methyl and bromo analogues, **8** and **5**, consume 100 mol % of periodate and undergo both oxidative rearrangement and enol oxidation (Scheme II) with ~15 min required for completion of oxidation, whereas methoxy analogue **15** and ethoxycarbonyl analogue **18** consume an initial 200 mol % of periodate within a few minutes. The oxidative rearrangement reaction is excluded for both **15** and **18**; **15** undergoes enol oxidation according to Scheme II, but the products of oxidation of **18** remained at this point undefined.

Scheme II. Application of Enol Oxidation Mechanism of Scheme I to α-Keto γ-Lactams 1, i.e., via Path a of Scheme III



The oxidation of **18** was carried out by very rapid addition of a methanol solution of **18** to a vigorously stirred buffer containing 200 mol % of periodate. After recovery of 35% of starting material, a major product, **19**, was isolated by chromatography. This slightly unstable oil differed in composition from **18** only by the absence of one carbon atom. The spectra of **19** resembled those of enol oxidation products **7**, **10**, and **16**, with the notable exception that the NMR spectrum displayed a somewhat broadened singlet at δ 8.1, which remained after exposure of **19** to D_2O. On the basis of these data, this material was assigned structure **19**. An alternative enol oxidation mechanism must then be operative, and the existence of this alternative mechanism is demonstrated further by the isolation of an analogous product **20** from the oxidation of methyl



analogue **8** in aqueous acetic acid. The structural assignments for **19** and **20** are further supported by the presence of characteristic *N*-formyl absorptions in their ^{13}C NMR spectra, and the structure of **20** was confirmed by synthesis. Pipecolic acid was formylated by the mixed anhydride method, and the

Table I. Product Distribution from Periodate Oxidation of α-Keto γ-Lactams 1 in Water, pH 6.3

compd	registry no.	yield (%) of products from each oxidation mode: path a	registry no.	path b	path c
15	66551-93-7	65[a] (100)[b]	66551-94-8	0	0
5	54409-79-9	12[c] (60)[b]	66551-95-9	40	0
8	54409-78-8	45[d] (50)[b]	66551-96-0	50	0
21	35620-54-3	*e*		70	*e*
18	54409-76-6	0		0	32[f,g] (100)[b]

[a] Isolated yield of **16**, based on **14**. [b] Projected yield; see text for discussion. [c] Isolated yield of **7**. [d] Isolated yield of **10**. [e] No attempt was made to account for remaining material. [f] Isolated yield of **19**. [g] Registry no. 66551-97-1.

methyl ketone was prepared from the acid via the β-keto ester, as previously described.

Thus we find three possible oxidative modes for lactams **1**. These are designated as enol oxidation path a (attack at enolic oxygen, Scheme II), ring contraction path b, and a new enol oxidation mode path c (attack at enolic carbon). These three modes are depicted in Scheme III, and the yields of products from the various lactams are summarized in Table I. Yields of β-lactam (path b) refer to isolation of the product as carboxylic acid;[1] yields in parentheses are projected yields with qualifications as discussed below.

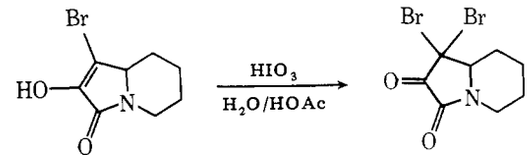
The isolated yield of oxamic acid **16** from oxidation of methoxylactam **15** was 65%, based on **14**; however, **15** decomposed in part during isolation. It is therefore likely that all of **15** which reacted with periodate was oxidized via path a, particularly in view of the absence of β-lactam formation.

From the oxidation of bromolactam **5**, β-lactam esters **6** were isolated in 26% yield, and oxalyl derivative **7** was isolated in only 12% yield. However, saturation of the reaction solution with salt and extraction at pH 2 gave an additional 35% yield of a mixture of β-lactam acids and ester–acids of **7**. This result and the phenolic character of **5** suggests that none of **5** was enol oxidized via path c.

Oxidation of methyllactam **8**, followed by esterification, gave β-lactam **9** and methyl ketone **10** in 35 and 45% yield, respectively, for a combined yield of 80%, which corresponds with reported yields for esterfication.[5] All present oxidations were carried out by adding substrate as a solution in methanol (or in THF, in the case of **5**), a procedure which lowers slightly the yield of β-lactam, whereas the yields of β-lactam (path b) given in Table I are from oxidation without use of cosolvent. The presumed enol oxidation yields from **5** and **8** are projected to no cosolvent reactions. In view of these yields, it appears that **8** was oxidized via its enol under these conditions only via path a, as in the case of **5**.

Considering the procedure used for the production of formyl derivative **19**, this compound is quite likely the initial product of oxidation of ethoxycarbonyllactam **18**. Reexposure of **19** to the oxidation conditions resulted in further oxidation as would be expected since **19** is an α-ketoacyl derivative. Regardless of whether **19** is the only initial product of oxidation, the absence of β-lactam formation and the pattern revealed by oxidation of the other lactams **1** suggest that **18** was oxidized only via path c.

As noted earlier, the initially inexplicable results of the oxidation of **8** with periodic acid in THF or in aqueous acetic acid, or with tetrabutylammonium periodate in chloroform/methanol, suggested that iodate, formed on initial oxidation by periodate, might be involved in some essential way. This proposal prompted a cursory examination of the reactivity of enols **1** with iodate. Both analogues **5** and **8** were oxidized by iodate in aqueous acetic acid, whereas the more acidic analogue **18** was unreactive (analogues **15** and **21** were not tested). Since **5** gave dibromo compound **22**, the oxidation very likely

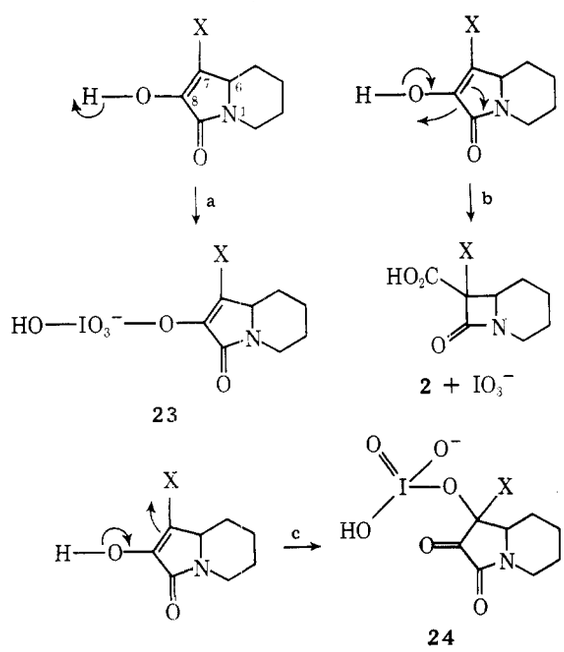


5 **22**

proceeds via a radical mechanism.[19] The extent to which oxidation by iodate competes with oxidation by periodate under acidic or nonaqueous conditions was not determined, but it appears that these conditions allowed for a relatively rapid oxidation of **8** by the iodate initially produced.

The possibility that other glycol cleaving reagents might be capable of inducing oxidative rearrangement was investigated. Exposure of methyl analogue **8** to sodium bismuthate in acetic acid containing phosphoric acid, and to lead tetraacetate in acetic acid, resulted in oxidation, but no β-lactam formation. The same was true for oxidation of the unsubstituted analogue **21** with lead tetraacetate in acetic acid.

Scheme III. Periodate Oxidation Modes for α-Keto γ-Lactams 1



Discussion

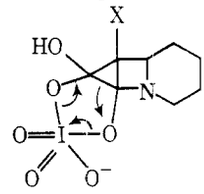
The enolic portion of lactams **1** offers three atoms at which oxidation could be initiated: the enolic oxygen, the α carbon (C-8), and the β-enolic carbon (C-7). In the case of methoxy analogue **15**, the methoxy group on the β carbon can be expected to induce increased electron density on the enolic oxygen, while in the case of ethoxycarbonyl analogue **18**, the opposite effect of electron withdrawal would lead to increased electron density on the β carbon. For the analogues **5**, **8**, and **21** electron distribution over the three-atom enolic system would be intermediate between the extremes represented by **15** and **18**.

A frequently proposed path for enol oxidation[6,8] begins with oxidation of the enolic oxygen by formation of a periodate ester as depicted in path a of Scheme III. Oxidative rearrangement to β-lactams **2** involves oxidation at the α carbon (C-8), as indicated in path b of Scheme III. We propose that the alternative mechanism for enol oxidation, the mechanism by which ethoxycarbonyl analogue **18** is oxidized, begins with oxidation of the β-enolic carbon (C-7) as indicated in path c of Scheme III. The relative rates of oxidation via each of the three paths a, b, and c can then be viewed as depending on electron density at each of the three atoms of the enolic portion of **1**.

A generalized form of oxidation via path a of Scheme III is given in Scheme I. For oxidation of reductone-like structures, X = Y = oxygen. For oxidation of compounds such as phenols and flavonols, X = oxygen and R does not equal a heteroatom bonded to a proton. When the reductone-like compound, catechol, was oxidized in $H_2{}^{18}O$, the resulting quinone was not labeled; however similar oxidation of a water-soluble guaiacol derivative (R = OCH_3; X = O) led to incorporation of label into the resulting quinone and not into the methanol released during oxidation.[8] The mechanism depicted in Scheme I gains further support in that it explains the products obtained from the oxidation of flavonols[11b] and some types of phenols[12,13] with periodic acid in methanol, and the oxidation of indoles with sodium periodate in aqueous methanol has been rationalized by invoking a variant of this mechanism in which X = N.[14] Numerous other periodate hydroxylation reactions can be viewed as proceeding via some variant of Scheme I.[6]

Application of the mechanism depicted in Scheme I to oxidation of lactams **1** is illustrated in Scheme II. Solvent attack at C-7 of the intermediate periodate ester would result in an α-hydroxy ketone which in turn would be oxidized in a classical manner to yield an oxalyl residue on the nitrogen and a carbonyl oxygen on what began as C-7 of **1**. This mechanism accounts for the exclusive product obtained from the 7-methoxy compound **15**, and the non-β-lactam products obtained from the 7-bromo and 7-methyl compounds **5** and **8** when oxidized under neutral conditions.

The proposed mechanism for oxidative rearrangement (path b of Scheme III) has been discussed[15] and involves oxidation of the α carbon (C-8) via two types of key intermediates, illustrated by structures **25** and **26** for the examples of lactams **1**. Oxidation via a hydroxycyclopropenone was invoked as a minor pathway in order to explain some scrambling of label in the product obtained from oxidation of 2-^{14}C-1-



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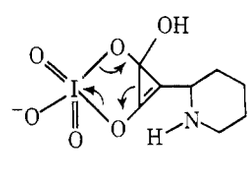

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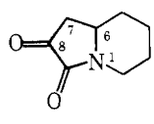

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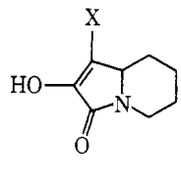
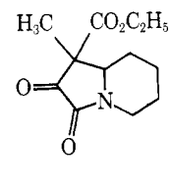


1, X ≠ H



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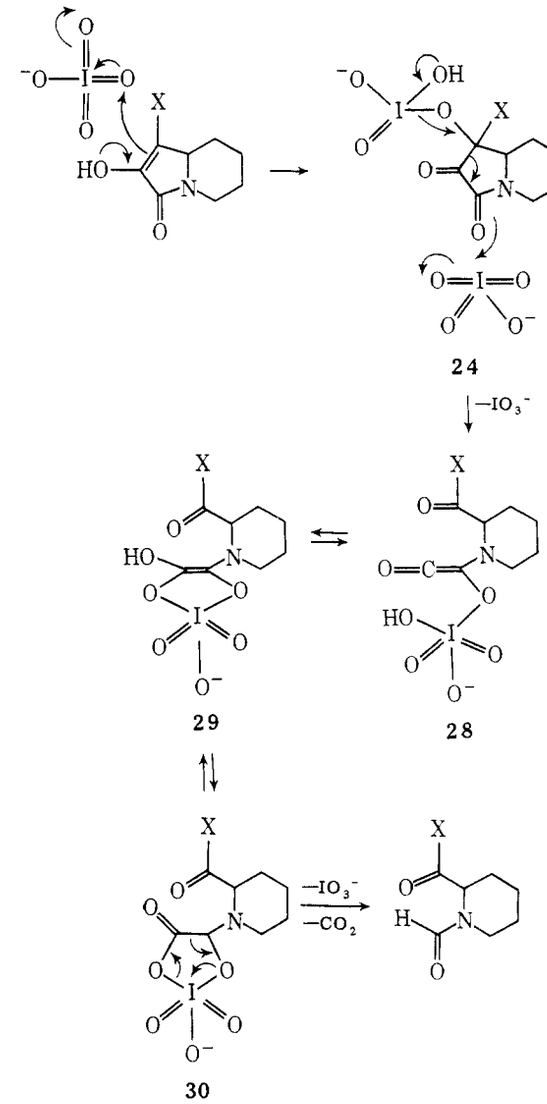
methyl-2,3-piperidinedione.[15] The proposed minor pathway cannot be operative unless both substituents on C-7 are hydrogen.

Neither oxidative rearrangement nor enol oxidation (either mode) can take place unless at least one proton is present on the β carbon (C-7). Thus lack of reactivity toward periodate observed in the case of the β-disubstituted derivative **27** not only confirms the inability of such a compound to undergo either rearrangement or hydroxylation but also indicates a resistance toward classical α-diketone-like cleavage.

Scheme IV. Mechanism of Enol Oxidation of α-Keto γ-Lactams 1 via Path c of Scheme III



24

29

28

30

Enol oxidation according to path c of Scheme III can be viewed as an example of the indicated general pattern[6] in which $R_nC^{\delta-}$ is added to the already known examples of Z = N, P, or S.

$$R_nZ: + IO_4^- \rightarrow R_nZ{=}O + IO_3^-$$

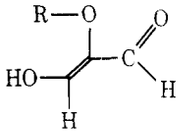
This generalization has been applied to sulfoxide formation[20] and oxidation of polycyclic aromatic hydrocarbons,[21] and the same representation has been offered as one of several rationalizations of some phenol oxidation results which appear anomalous without some alternative to oxidation via path a of Scheme III.[12]

Application of this generalization to oxidation of lactams **1** is depicted in Scheme IV. In most cases the only available path for collapse of an intermediate such as **24** would be to leave the electron pair on the C-7 oxygen, protonation of which would lead, for the case of lactams **1**, to the same α-hydroxy ketone produced according to Scheme II. But in the case of lactams **1**, the juxtaposition of the lactam carbonyl allows for an alternative mode of collapse which in turn allows for an alternative mode for a second oxidation step. Collapse of **24** as indicated in Scheme IV is aided by a concomitant oxidation to the periodate ester **28**, which in turn could form the cyclic

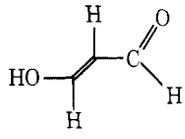
intermediate **29**. Tautomerization of **29** leads to **30**, which can now collapse to product by expulsion of carbon dioxide and iodate. This mechanism accounts for the products formed from the 7-ethoxycarbonyl compound **18** when oxidized under neutral aqueous conditions and from the 7-methyl compound **8** when oxidized under acidic conditions.

The products obtained from lactams **1** when oxidized under neutral aqueous conditions demonstrate the influence exerted by the β-substituent X on the relative rates of oxidation via the paths a, b, and c of Scheme III. The influence of the reaction medium on these relative rates is illustrated by isolation of products of all three paths from oxidation of methyl analogue **8**: under neutral aqueous conditions paths a and b were followed, whereas under acidic conditions the oxidation mode changed to path c.

The potential of the dual mechanism picture provided by enol oxidation paths a and c of Scheme III for development of a unified explanation for periodate hydroxylation reactions is clear from consideration of the morass of reactions referred to in the carbohydrate literature as non-Malapradian or "over-oxidation" reactions. Reactions to which these names are attached generally involve oxidation of substituted or unsubstituted malonaldehydes, malonic acids, and related derivatives. Using malonaldehydes as the example, these compounds are generally one or the other of two types, **31** or **32**. Comparison with lactams **1** reveals **32** as analogous to lactam **18** in that both contain an electron withdrawing group positioned so as to induce increased electron density on the α carbon of the enol (the middle carbon of **32**). On the other hand, the substituted malonaldehyde **31** contains an electron donating oxygen substituent in addition to the electron withdrawing aldehyde. Thus it would not be surprising if compounds such as **31** display reactivity analogous to that of enols **15**, **5**, and **8**, reacting with periodate via path a of Scheme III and showing substantial reactivity toward iodate. It would likewise be expected that compounds such as **32** would display reactivity analogous to that of **18**, reacting with periodate via path c of Scheme III and showing greatly reduced or no reactivity toward iodate. Although the initial product from compounds such as **31** or **32** when oxidized by periodate in aqueous medium would be the same in any case, the reactivity patterns generally observed[22] correspond to those expected.



31



32

Experimental Section[23]

Oxidation of 7-Bromo-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]-non-7-ene (5). Lactam **5**[1] (1.3 g, 5.5 mmol) was added as a solution in THF (20 mL) over 10 min to a rapidly stirred buffer prepared as described previously (0.2 M, pH 6.3, 275 mL)[1] containing $NaIO_4$ (2.35 g, 11.0 mmol) and cooled to 6–7 °C. After completion of oxidation the solution was treated at room temperature with TEOF[24] (45 g, 230 mmol), added in portions over 40 min with pH maintained at 6–7 by addition when needed of $NaHCO_3$. The solution was then extracted with ethyl acetate (3 × 100 mL), and the combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel (40 g) with $CHCl_3$ and then on kieselgel (150 g) with ether–petroleum ether (bp 30–60 °C) (3:1 v/v) gave ethyl oxalyl piperidide **7** (174 mg, 12%), the major isomer of **6** (348 mg, 23%), and the minor isomer of **6** (51 mg, 3%). NMR and IR spectra of the isomers of **6** corresponded where appropriate with the spectra of the corresponding methyl esters.[1] Ethyl oxalyl piperidide **7** was purified by bulb-to-bulb distillation at bath temperature 130 °C (0.01 mm): IR 1737, 1661 cm^{-1}; NMR δ 1.1–2.0 (11 H, m), 2.0–2.5 (1 H, m), 2.6–3.8 (2 H, m), 4.27 (4.4 H, m), 5.18 (0.6 H, m); mass spectrum *m/e* (rel intensity) 257 (M^+, 6%), 220 (11), 184 (39), 176 (19), 156 (66), 128 (14), 91 (100).

Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.0; H, 7.4; N, 5.4. Found: C, 55.9; H, 7.4; N, 5.4.

Ethyl Oxalyl 2-Ethoxycarbonylpiperidide (7). Fuming sulfuric acid (20 mL, 15%) was added dropwise and with stirring to a solution of pipecolic acid (4.6 g, 36 mmol) in absolute ethanol (100 mL). The solution was refluxed for 20 h and then cooled. Aqueous sodium hydroxide (2 M, 200 mL) was added with cooling until the pH reached 6–7, followed by K_2CO_3 (41 g). The mixture was extracted with ether (3 × 150 mL), and the combined extracts were dried, evaporated, and distilled (bp 55 °C (1.4 mm) [lit.[25] bp 91–93 °C (9 mm)]) to yield 3.53 g (63%). Ethyl oxalyl chloride (273 mg, 2.0 mmol) in CH_2Cl_2 (1.0 mL) was added with stirring to the ethyl pipecolate (636 mg, 4.0 mmol) in CH_2Cl_2 (2.0 mL) at room temperature. After being stirred for 10 min, water (15 mL) and ether (15 mL) were added and the pH was adjusted to 2 with 10% HCl (1 mL), then the phases were shaken and separated. The ether layer was washed with saturated $NaHCO_3$ (10 mL) and then with brine (7 mL), dried ($MgSO_4$), and evaporated to yield 442 mg (86%) of **7**, identical with material obtained from the oxidation of bromo analogue **5** by NMR, IR, and TLC comparison.

Hydrogen Oxalyl 2-Methoxycarbonylpiperidide (16) from 5. From an oxidation of **5** in which **5** had been added as a solution in CH_3OH as described previously,[1] there was isolated by continuous extraction with CH_2Cl_2 at pH 2 a mixture of acids, part (418 mg) of which was chromatographed on kiesegel (25 g) with petroleum ether (bp 30–60 °C), ethyl acetate, acetic acid (18:27:5 v/v) to yield **16** (101 mg), which was recrystallized from $CHCl_3$–hexanes: mp 114–116 °C; IR 1740, 1727 (shoulder), 1660 cm^{-1}; NMR δ 1.1–2.0 (5 H, m), 2.0–2.5 (1 H, m), 2.7–3.7 (2 H, m), 3.87 and 3.90 (3 H, singlets), 4.33 (0.1 H, m), 4.57 (0.3 H, m), 5.27 (0.6 H, m), 10.9 (1 H, s); mass spectrum *m/e* (rel intensity) 215 (M^+, 7%), 170 (59), 142 (34), 128 (88), 55 (100).

Anal. Calcd for $C_9H_{13}NO_5$: C, 50.2; H, 6.1; N, 6.5. Found: C, 50.2; H, 6.2; N, 6.6.

Oxidation of 7-Methyl-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]-non-7-ene (8). Ethyl Oxalyl 2-Acetylpiperidide (10). Lactam **8**[1] (200 mg, 1.2 mmol) was added as a solution in THF (4 mL) and CH_3OH (0.5 mL) over 10 min at room temperature to a rapidly stirred buffer prepared as described previously (0.2 M, pH 6.3, 60 mL)[1] containing $NaIO_4$ (514 mg, 2.4 mmol). After completion of oxidation (15 min) the solution was treated with TEOF (11 g, 84 mmol) as described in the oxidation of **5**. The solution was then extracted with ethyl acetate (3 × 30 mL), and the combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel (30 g) with $CHCl_3$ gave **10** (74 mg), an intermediate fraction (84 mg) of **10** and **9** determined by NMR inspection to contain 45 mol % of **9**, then **9** (53 mg), NMR and IR of which corresponded where appropriate with the spectra of the methyl ester.[1] Oxalyl piperidide **10** was purified by bulb-to-bulb distillation, bath temperature 120 °C (0.01 mm): IR 1742, 1727, 1661 cm^{-1}; NMR δ 1.0–1.9 (8 H, m), 1.9–2.5 (1 H, m), 2.20 and 2.24 (3 H, singlets), 3.6 (2.5 H, m), 4.4 (2 H, m), 5.1 (0.5 H, m); mass spectrum *m/e* (rel intensity) 227 (M^+, 1%), 184 (54), 156 (71), 154 (13), 43 (100).

Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.1; H, 7.5; N, 6.2. Found: C, 57.9; H, 7.4; N, 6.0.

Benzyl Pipecolate. Benzyl pipecolate has been prepared previously in 8% yield by reaction of pipecolic acid with benzyl alcohol and thionyl chloride.[26] The following procedure gives the desired ester in good yield.

A mixture of toluene (50 mL), pipecolic acid (5.2 g, 40 mmol), benzyl alcohol (21 g, 195 mmol), and *p*-toluenesulfonic acid (9.6 g, 50 mmol) was heated under reflux for 60 h with removal of water. The clear orange solution was added to water (150 mL) and shaken, and the aqueous phase was subsequently washed with ether (3 × 75 mL) and then made alkaline by addition of excess saturated aqueous sodium carbonate. The solution was extracted with ether (3 × 75 mL) and the organic portions were combined and dried ($MgSO_4$). After filtration the ether was removed to yield benzyl pipecolate as a yellow oil (6.3 g, 72%). IR and NMR spectra of this material were identical with the reported spectra.

Ethyl Oxalyl 2-Benzyloxycarbonylpiperidide. A solution of benzyl pipecolate (6 g, 27 mmol) in dry ether (50 mL) and triethylamine (10.1 g, 100 mmol) was cooled in an ice–water bath, then a solution of ethyl oxalyl chloride (4.2 g, 30 mmol) in dry ether (20 mL) was added over 0.5 h, taking precautions for the exclusion of moisture. The resulting slurry was stirred at room temperature for a further 2 h and then added to a saturated aqueous sodium carbonate solution (50 mL); when CO_2 evolution had ceased the ether layer was separated and washed with 1 M hydrochloric acid (2 × 50 mL) and again with saturated aqueous sodium carbonate (50 mL). The organic layer was dried ($MgSO_4$) and after filtration the ether was removed by evaporation to yield benzyl 1-(ethyl oxalyl)pipecolate (7.33 g, 84%). Dis-

tillation (170 °C (0.15 Torr)) yielded the product as a yellow oil (6.1 g, 70%): IR 1660, 1735 cm^{-1}; NMR δ 1.10–2.00 (8 H, m), 2.05–2.60 (1.4 H, m), 3.20–3.80 (1.6 H, m), 4.35 (2.4 H, q), 5.15 (2.6 H, s), 7.40 (5 H, s).

Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.9; H, 6.6; N, 4.4. Found: C, 64.0; H, 6.6; N, 4.4.

Ethyl Oxalyl 2-Carboxypiperidide. Ethyl oxalyl 2-benzyloxycarbonylpiperidide (3.2 g, 10 mmol) in dry ethanol (30 ml) and 10% Pd/C (0.4 g) were shaken with hydrogen for 30 min after which the suspension was filtered through celite, the ethanolic filtrate was evaporated, and the residue was dissolved in excess saturated sodium carbonate solution. This solution was washed with ether (2 × 20 mL) and then acidifed to pH 1 with 1 M hydrochloric acid and extracted with ether (3 × 50 mL). The combined ether extracts were dried ($MgSO_4$) and filtered and the ether was removed by evaporation to yield ethyl oxalyl 2-carboxypiperidide (1.49 g, 65%) as a colorless oil: IR 1625, 1735 cm^{-1}; NMR δ 1.00–2.00 (8 H, m), 2.15–2.70 (1 H, m), 3.00–3.85 (2 H, m), 4.40 (2.3 H, q), 5.15 (0.7 H, br s), 10.05 (1 H, s).

Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.4; H, 6.6; N, 6.1. Found: C, 52.3; H, 6.6; N, 6.1.

Repeating this experiment to the point of evaporation of the ethanolic filtrate gave ethyl oxalyl 2-carboxypiperidide (99% yield) whose IR and NMR spectra were identical to those obtained above and which could be used without any further purification.

Ethyl Oxalyl 2-(2-*tert*-Butoxycarbonyl)acetylpiperidide. To a stirred solution of *tert*-butyl hydrogen malonate (0.47 g, 2.93 mmol) in dry THF (10 mL) was added isopropylmagnesium bromide (5.56 mmol, as a 0.83 M solution in THF). After initial gas evolution had subsided the solution was heated under reflux until the cessation of further gas evolution (ca. 3 h).

To a stirred solution of ethyl oxalyl 2-carboxypiperidide (0.67 g, 2.93 mmol) in dry THF (10 mL) was added solid carbonyldiimidazole (0.52 g, 3.2 mmol) in portions over 5 min and the solution was stirred at room temperature for 1 h after which time all gas evolution had ceased. This solution was added over 5 min to the ice–water bath cooled solution of the magnesium salt of the dianion of *tert*-butyl hydrogen malonate prepared previously, the resulting solution was allowed to come to room temperature, and stirring was continued for a further 2 h. Ether (50 mL) was added and the resulting suspension was decomposed by the addition of 1 M hydrochloric acid (25 mL). The organic layer was separated and washed with 1 M hydrochloric acid (20 mL) and saturated aqueous sodium bicarbonate (2 × 25 mL) and dried ($MgSO_4$). After filtration the solvents were removed to yield ethyl oxalyl 2-(2-*tert*-butoxycarbonyl)acetylpiperidine (0.54 g, 58%): NMR δ 1.00–2.25 (18 H, m), 2.30–3.20 (2 H, br m), 3.52 (2 H, d), 4.40 (2.3 H, q), 5.15 (0.7 H, br s). Attempted purification of this material by bulb-to-bulb distillation (95–105 °C (0.3 mm)) led to decomposition.

Ethyl Oxalyl 2-Acetylpiperidide (10). Ethyl oxalyl 2-(2-*tert*-butoxycarbonyl)acetylpiperidide (0.52 g, 1.6 mmol) was reacted in boiling toluene (15 mL) containing *p*-toluenesulfonic acid (0.05 g, 0.26 mmol) for 2 h. Ether (25 mL) was added to the cooled solution and this was washed with saturated aqueous sodium carbonate (2 × 25 mL) and 0.5 M hydrochloric acid and dried ($MgSO_4$).

After filtration the solvents were removed by evaporation to yield a crude product (0.24 g, 65%) which was purified by bulb to bulb distillation (95–100 °C (0.3 mm)) to yield **10** as a colorless oil (0.18 g, 49%), identical with material obtained from the oxidation of **8** by NMR, IR, and TLC comparison.

Oxidation of 8 in Aqueous Acetic Acid. Periodic acid dihydrate (137 mg, 0.6 mmol) dissolved in water (0.5 mL) was diluted with acetic acid (6 mL). Compound **8** (50 mg, 0.30 mmol) in acetic acid (1 mL) was then added over a period of 2 min. After 1.4 h ethylene glycol (28 mg, 0.45 mmol) in acetic acid (1 mL) was added, resulting, after a few seconds, in a quite cloudy solution. The solution was filtered through cotton/celite, rinsing with $CHCl_3$, then the solvents were evaporated. The residue was purified by bulb-to-bulb distillation, bath temperature 70–100 °C (0.05–0.10 mm). At the higher end of the temperature range a solid started subliming out; the distillation was stopped at this point, yielding **20** (18 mg, 32%), identical with material prepared according to the following procedure by NMR, IR, and TLC comparison.

1-Formyl-2-carboxypiperidine. Pipecolic acid (5 g, 38.8 mmol) was stirred at room temperature in formic acid (100 mL, 95–97%), and acetic anhydride (30 mL) was added over 0.5 h, causing the temperature to rise to 50–55 °C. After stirring for a further 4 h, ice–water (80 mL) was added and the aqueous acidic solvents were removed by evaporation under reduced pressure. Further drying at 60 °C (2 mm) yielded crude product (6 g, 99%) as a gum which slowly solidified over 48 h: mp 79–82 °C; NMR δ 0.85–1.95 (5 H, m), 1.95–2.45 (1 H, m), 2.50–3.20 (0.5 H, m), 3.20–3.80 (1.5 H, m), 4.00–4.50 (0.5 H m), 4.90–5.20 (0.5 H, m), 8.00 and 8.05 (1 H, s), 11.20 (1 H, br s). This material was carried on to the next stage without further purification.

1-Formyl-2-(2-*tert*-butoxycarbonyl)acetylpiperidine. To a stirred solution of *tert*-butyl hydrogen malonate (2.23 g, 13.9 mmol) in dry THF (30 mL) was added isopropylmagnesium bromide (26.5 mmol, as a 0.97 M solution in THF). After initial gas evolution had subsided the solution was heated under reflux for 3 h.

To a stirred solution of 1-formyl-2-carboxypiperidine (2.19 g, 13.9 mmol) in dry THF (30 mL) was added solid carbonyldiimidazole (2.6 g, 16 mmol) in portions and the solution was stirred at room temperature with the exclusion of moisture for 1 h. This solution was then added over 0.5 h to the previously prepared solution of the magnesium salt of the dianion of *tert*-butyl hydrogen malonate with ice–water bath cooling. The resulting milky white suspension was allowed to come to room temperature and stirred for a further 15 h. Ether (50 mL) was then added and the suspension was decomposed by the addition of 1 M hydrochloric acid (20 mL). When the mixture had formed two clear layers the organic portion was separated and washed with 1 M hydrochloric acid (2 × 40 mL) and saturated aqueous sodium carbonate (25 mL) and dried ($MgSO_4$). After filtration the solvents were evaporated to yield the desired product (0.89 g, 25%) as a colorless oil. NMR confirmed this compound as the major product with absorptions at δ 1.50 (*tert*-butyl), 3.40 ($COCH_2CO_2$-*t*-Bu), and 8.15 (NCHO), but absorptions at δ 3.20 and 2.22 suggested that partial cleavage of the *tert*-butyl group and subsequent decarboxylation had occurred during workup. The material was carried to the next stage with no further purification.

1-Formyl-2-acetylpiperidine (20). The preceding mixture (1.09 g) was stirred in trifluoroacetic acid (10 mL) at room temperature for 5 h after which time the acid was removed by evaporation at 40 °C under reduced pressure to yield crude 1-formyl-2-(2-carboxy)acetylperidine (0.85 g) as an orange-brown gum. Complete cleavage of the *tert*-butyl group was confirmed by NMR. This gum was vigorously stirred as a suspension in boiling toluene (10 mL) for 1 h during which time a homogeneous solution was formed. The toluene was removed by evaporation to yield a crude product (0.59 g) as a brown oil. Chromatography of this material (30 g silica, eluting with ether) yielded a mixture of compounds (0.06 g) as the first major fraction, followed by **20** (0.48 g, 72%) as a colorless oil: IR 1725, 1665 cm^{-1}; NMR δ 0.90–2.58 (6 H, m), 2.18 and 2.20 (3 H, s), 2.60–3.80 (1.8 H, m), 4.05–4.55 (0.5 H, m), 4.85–5.10 (0.7 H, br s), 8.05 and 8.10 (0.9 H, s); ^{13}C NMR δ 205.08 (keto), 162.15 and 161.61 (formyl); mass spectrum *m/e* (rel intensity) 155 (M^+, 2%), 112 (100); high resolution mass spectrum, calcd for $C_8H_{13}NO_2$ (M^+), 155.0946 found, 155.0944.

Ethyl 3-Methoxy-3-*tert*-butoxycarbonyl-2-oxopropionate (12). To absolute ether (100 mL) and isopropylcyclohexylamine (14.3 g, 0.10 mol, freshly distilled from CaH_2), cooled in a dry ice/acetone bath, *n*-butyllithium (35.7 mL, 2.80 M) was added dropwise over 8 min, and the solution was stirred for 30 min. Then *tert*-butyl methoxyacetate[27] (14.6 g, 0.10 mol) in absolute ether (60 mL) was added rapidly over 6 min, the cooling bath was removed after 1 h, and diethyl oxalate (14.61 g, 0.10 mol, freshly distilled from CaH_2) in absolute ether (15 mL) was added over 5 min. After the addition was completed, the mixture was held at room temperature for 20 min and then at 50 °C for 0.5 h. The clear solution was then cooled in an ice bath, a solution of 6 N HCl (40 mL) diluted to 80 mL with ice was added, the layers were separated, and the acidic aqueous layer was further extracted with ether (3 × 50 mL). The combined extracts were washed with brine (75 mL) and with saturated $NaHCO_3$ (50 mL), dried ($MgSO_4$), and evaporated to give 23.3 g, 18.4 g of which was distilled through a vacuum jacketed column to give **12** (12.0 g, 62%, bp 88–89 °C (0.1 mm)) which was purified further by bulb-to-bulb distillation, bath temperature 75–90 °C (0.02 mm)): IR 1764, 1733, 1656 (w) cm^{-1}; NMR (absorptions were split due to an enol content of ~10%) keto form, δ 1.38 (3 H, t), 1.47 (9 H, s), 3.57 (3 H, s), 4.38 (2 H, q), 4.88 (1 H, s), and enol form, 1.58 (9 H, s), 3.67 (3 H, s), 4.35 (2 H, q), 10.87 (1 H, s).

Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.6; H, 7.4. Found: C, 53.4; H, 7.6.

7-Methoxy-7-*tert*-butyoxycarbonyl-8,9-dioxo-1-azabicyclo[4.3.0]nonane (14). An ethanol/ether solution (50 mL) of Δ^1-piperideine (**13**) was prepared as described previously[1] from piperidine (3.4 g, 40 mmol) and cooled in an ice bath. With continued cooling and with rapid stirring a solution of ester **12** (4.92 g, 20 mmol) in absolute ethanol (34 mL) was added rapidly over 10 min. After completion of addition the cooling bath was removed and the solution was stirred at room temperature for 6 h. Acetic acid (1.2 g, 20 mmol) was added and then the reaction solution was evaporated. The residue was taken up in CH_2Cl_2/water (100 mL of each), the layers were separated,

and the aqueous layer was further extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give a crude residue which was chromatographed on silica gel (50 g) with $CHCl_3$ to give **14**: 2.33 g, 30%; mp 119.5–120.5 °C after crystallization from $CHCl_3$–hexane; IR 1773, 1745, 1718 cm^{-1}; NMR δ 1.2–2.3 (6 H, m), 1.48 (9 H, s), 2.93 (1 H, m), 3.60 (3 H, s), 3.83 (1 H, dd, J = 4, 10 Hz), 4.45 (1 H, br dd, J = 13 Hz).

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.3; H, 7.5; N, 4.9; Found: C, 59.3; H, 7.3; N, 4.9.

7-Methoxy-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (15). To *tert*-butyl ester **14** (90 mg, 0.32 mmol) in acetic acid (0.4 mL) was added acetic acid saturated with HBr (6.0 mL). After being stirred at room temperature for 10 min, the solvent was evaporated under reduced pressure at room temperature. The residue was taken up in $CHCl_3/CH_3OH$, the solvent was evaporated, the residue was then dissolved in CH_2Cl_2 and dried ($MgSO_4$), and the solvent was evaporated to give crystalline residue: mp 117–122 °C dec; IR 3125 (br), 1667 (br) cm^{-1}; NMR δ 1.0–2.6 (6 H, m), 3.17 (1 H, m), 3.7–4.5 (2 H, m), 4.25 (3 H, s), 9.47 (1 H, s); mass spectrum *m/e* (rel intensity) 183 (M^+, 60%), 168 (37), 152 (100); high resolution mass spectrum, calcd for $C_9H_{13}NO_3$ (M^+), 183.0895, found, 183.0896.

Oxidation of 15. The *tert*-butyl ester **14** (283 mg, 1.0 mmol) was converted to **15** as described above, then the residue was added as a solution in CH_3OH (2.5 mL) to a pH 6.3 buffer (50 mL, prepared as described previously)[1] containing sodium periodate (428 mg, 2.0 mmol) over a period of 4 min. A UV spectrum of an aliquot removed 3 min later indicated that all of the periodate had been consumed. Oxidant was destroyed as described[1] with $NaHSO_3$ (832 mg, 8.0 mmol), and after adjustment of the pH to 6, the solution was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were dried ($MgSO_4$) and evaporated to yield a residue of 23 mg. The aqueous layer was then adjusted to pH 3.0 with 3.0 M phosphoric acid, saturated with sodium chloride (pH 2.0), and extracted with three 50-mL portions of $CHCl_3$ and then continuously to yield after drying ($MgSO_4$) 140 mg (65%) of **16**, identical with that described above by IR, NMR, and TLC comparison.

Oxidation of 7-Ethoxycarbonyl-8-hydroxy-9-oxo-1-azabicyclo[4.3.0]non-7-ene (18). Formation of 19. A solution of **18**[1] (1.0 g, 4.44 mmol) in CH_3OH (10 mL) was added in one portion to a vigorously stirred buffer at pH 6.3 (40 mL) and at 18 °C containing $NaIO_4$ (1.71 g, 8 mmol). Reaction as evidenced by gas evolution was apparent. A starch–iodide test after 3 min showed complete consumption of periodate and the remaining oxidants were destroyed in the usual manner.[1] The solution (now at pH 2) was saturated with NaCl and extracted with chloroform (3 × 100 mL); the combined extracts were dried ($MgSO_4$) and filtered and the solvents were removed by evaporation to yield a mixture of oxidation products and starting material (1 g).

Chromatography of this material (50 g of silica/ether) yielded initial fractions which NMR suggested to be a mixture of one major and several minor components (total weight 0.6 g); the next material to be eluted was unreacted **18** (0.35 g). The mixture obtained from the previous chromatography was rechromatographed (30 g silica/CH_2Cl_2–5% ether) and the first fractions to be eluted were the major component of the mixture, 1-formyl-2-(ethyl oxalyl)piperidine (0.31 g, 32%): NMR δ 0.85–2.55 (9 H, br m with triplet centered at 1.40), 2.55–3.05 (0.5 H, br m), 3.15–3.78 (1.5 H, m), 4.02–4.60 (2 H, q), 4.70–4.90 (0.3 H, m), 5.16–5.57 (0.7 H, m), 8.05 (1 H, s); IR 1670, 1735 cm^{-1}; mass spectrum *m/e* (rel intensity) 213 (M^+, 2%), 185 (32), 154 (30), 126 (36), 112 (100), 83 (100), 56 (100), 55 (100); ^{13}C NMR δ 191.74 (keto), 162.61 and 161.91 (formyl). A sample for analysis was obtained by bulb-to-bulb distillation (110–120 °C (0.3 mm)).

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.3; H, 7.1; N, 6.6. Found: C, 56.0; H, 7.1; N, 6.4.

7,7-Dibromo-8,9-dioxo-1-azabicyclo[4.3.0]nonane (22). To $NaIO_3$ (75 mg, 0.38 mmol) dissolved in water (1.0 mL) was added acetic acid (6.0 mL), then **5** (70 mg, 0.30 mmol) in acetic acid (1.2 mL) was added with stirring over 2 min. After 1.2 h, the solution was evaporated at room temperature, CH_2Cl_2 (5 mL) followed by water (5 mL) was rapidly added with vigorous stirring, the layers were separated, and the aqueous layer was extracted further with CH_2Cl_2 (10 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a crystalline residue (55 mg) which was chromatographed on silica gel (0.5 g) with $CHCl_3$ to give **22** (31 mg): mp 139–142 °C dec; IR 1783, 1724 cm^{-1}; NMR δ 1.0–2.5 (6 H, m), 2.9 (1 H, m), 4.10 (1 H, dd, J = 4, 11 Hz), 4.35 (1 H, br dd, $J_{\alpha,\beta}$ = 13 Hz).

Anal. Calcd for $C_8H_9NBr_2O_2$: C, 30.9; H, 2.9; N, 4.5; Br, 51.4. Found: C, 31.2; H, 3.0; N, 4.4; Br, 50.9.

The Action of Periodate on 7-Ethoxycarbonyl-7-methyl-8,9-dioxo-1-azabicyclo[4.3.0]nonane (27). Compound **27**[1] (24 mg, 0.10 mmol) in CH_3OH (0.25 mL) was added to the usual buffer[1] at pH 6.3 (5 mL). No consumption of periodate was detected during the next hour. The solution was then extracted with CH_2Cl_2 (2 × 5 mL), and the combined extracts were dried ($MgSO_4$) and evaporated to yield 22 mg (91%), identical by IR comparison with starting material.

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Registry No.—*cis*-**6**, 66551-98-2; *trans*-**6**, 66551-99-3; **9**, 66552-00-9; **12**, 66552-01-0; **13**, 505-18-0; **14**, 66552-02-1; **20**, 66552-03-2; **22**, 66552-04-3; **27**, 42599-33-7; pipecolic acid, 535-75-1; ethyl pipecolate, 15862-72-3; ethyl oxalyl chloride, 4755-77-5; benzyl alcohol, 100-51-6; benzyl pipecolate, 38068-75-6; benzyl 1-(ethyl oxalyl)pipecolate, 66552-05-4; ethyl oxalyl 2-carboxypiperidide, 66552-06-5; *tert*-butyl hydrogen malonate, 40052-13-9; ethyl oxalyl 2-(2-*tert*-butyoxycarbonyl)acetylpiperidine, 66552-07-6; 1-formyl-2-carboxypiperidine, 54966-20-0; 1-formyl-2-(2-*tert*-butoxycarbonyl)acetylpiperidine, 66552-08-7; *tert*-butyl methoxyacetate, 17640-23-2; diethyl oxalate, 95-92-1.

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(18) During this study the use of pinacol and ethylene glycol for destruction of excess periodate was investigated. Pinacol was unreactive toward tetrabutylammonium periodate in chloroform in 67% (v/v) methanol in chloroform, whereas ethylene glycol was oxidated in both 10 and 67% (v/v) methanol in chloroform, with the rate of oxidation increasing with increasing concentration of methanol.
(19) Sodium iodate has been used occasionally for phenolic coupling (ref 7), and a radical mechanism has been invoked to explain cyclization of a pyrogallol derivative to the colchicine framework with sodium iodate [A. I. Scott, F. McCapra, J. Nabney, D. W. Young, A. J. Baker, T. A. Davidson, and A. C. Day, *J. Am. Chem. Soc.*, **85**, 3040 (1963)]. Iodine frequently appears during periodate and iodate oxidation, particularly in acid solution (ref. 6), and the combination of iodine and iodic acid is capable of causing iodination reactions (ref 7). Indeed, iodine containing products have resulted from periodic acid oxidation of phenols (ref 12) and methylcyclopentane-2,3-dione [G. Hesse and K. Mix, *Chem. Ber.*, **92**, 2427 (1959)]. The iodic acid oxidation product of **8** appeared to be a β-disubstituted derivative (as indicated by characteristic IR and NMR spectra) which did not proceed to an oxalic acid on exposure to sodium periodate. Therefore the product is probably the iodinated derivative.
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Chemistry of Heterocyclic Compounds. 29. Synthesis and Reactions of Multihetero Macrocycles Possessing 2,4-Pyrimidino Subunits Connected by Carbon–Oxygen and/or –Sulfur Linkages[1a]

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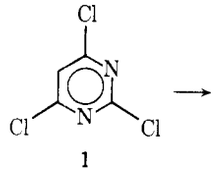
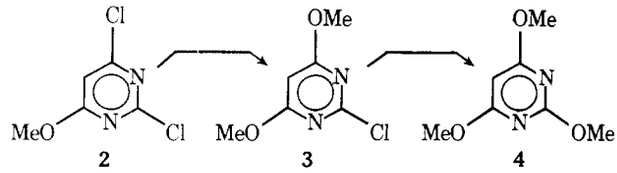
The 2,4-pyrimidino moiety has been incorporated into the "crown-ether" framework. 1:1 macrocycles have been characterized, whereas isomeric 2:2 and 3:3 macrocycles containing the 2,4-pyrimidino unit have been isolated and the isomeric distribution has been ascertained via NMR analysis. The 1:1 macrocycles (**11**, **12**, and **14**) undergo a facile Hilbert–Johnson reaction in the presence of methyl iodide at elevated temperature. Thermolysis of these 1:1 compounds causes a rearrangement to afford the corresponding uracil macrocycles. The CS and CSO 1:1 and 2:2 macrocycles have been prepared by similar procedures using the appropriate mercaptides.

In the course of our studies of multihetero macrocycles[2] which contain 2,6-pyridino,[3] 2,6-pyrazino,[4] 3,6-diazino,[5] and other heterocyclic subunits,[2] we have now investigated the inclusion of the 2,4-pyrimidino moiety. The general area of pyrimidines is so vast that it is beyond total review; however, Brown has made a Herculean effort to summarize the first 150 years of pyrimidine chemistry.[6,7] From a survey of pyrimidine chemistry, the inclusion of the pyrimidino moiety within a "crown-ether" framework has not been considered. The biological and medicinal interest in pyrimidines[8] affords further impetus to prepare this new type of macrocyclic system, the topic of this paper.

In view of the electron deficiency of the 2, 4, and 6 positions of the pyrimidine nucleus, halogen atoms located at these positions are susceptible to substitution by nucleophilic reagents. The general preparation of amines, ethers, and mercaptides, as well as a variety of other functions, at these positions on the pyrimidine ring is via direct displacement of chloride ion with the appropriate nucleophile.[9] Selective substitution can be also realized if the reaction conditions are controlled. For example, 2,4,6-trichloropyrimidine (**1**) reacts with sodium methoxide in methanol at 0 °C to generate **2**,[10] with 2 equiv at room temperature to give **3**,[11] and with 3 equiv at 70–100 °C to give 2,4,6-trimethoxypyrimidine (**4**).[11c,d] Thus,



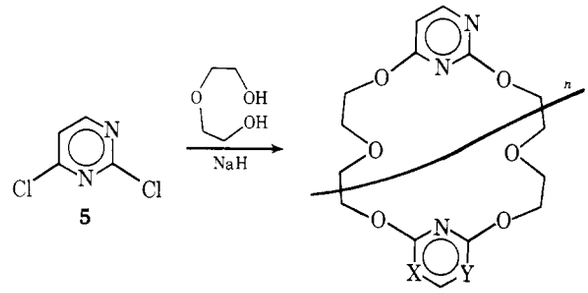
1



2 **3** **4**

initial 4 substitution of 2,4-dichloropyrimidine (**5**) should be preferred to 2 substitution by alkoxide ion;[12] however, the picture is less simple for polysubstituted pyrimidines.[9]

A. 2,4-Pyrimidino Macrocycles with Carbon–Oxygen Bridges. (1) Diethylene Glycol. Reaction of 2,4-dichloropyrimidine (**5**) with the dianion generated from anhydrous diethylene glycol and 2 equiv of sodium hydride afforded the 2:2 macrocycles **6** as the major cyclic products. When the reaction was conducted at 140 °C (in refluxing xylene), only numerous polymeric open-chain compounds were isolated but not characterized. At lower reaction temperatures (78 °C, refluxing benzene) the 3:3 macrocycle **7** was isolated along with **6**. Approximately equal amounts of the two dimers **6a** (mp 171–173 °C) and **6b** (mp 163–165 °C) were separated by careful thick-layer chromatography. Spectral data afforded little assistance in the structural assignment of these dimers[13] as well as trimer **7**; NMR chemical shift differences ($\Delta\delta$) were <0.1 ppm, and UV and IR data were nearly superimposible. The 1:1 C,O macrocycle **6** (n = 0) was not detected; however,



5

X ≠ Y = CH or N

6a,b, n = 1

7, n = 2

as experienced in our previous studies with this synthetic procedure,[3,5] only when the "meta" bridge possesses sulfur atoms with their diminished bond angles can the ten-membered ring be formed.

The structures of these C,O macrocycles were easily confirmed by molecular weight determination (mass spectrometry and/or osmometry) and ^{1}H NMR spectroscopy. The 5,6-pyrimidine hydrogens appear as doublets (J = 5 Hz) at δ 6.25–6.41 and δ 8.10–8.20, respectively, whereas the α methylenes appear as ill-defined triplets at δ 4.5–4.6.

(2) Triethylene Glycol. When 2,4-dichloropyrimidine (**5**) was treated with the disodium salt of triethylene glycol in refluxing xylene, the desired 1:1 macrocycle **8** was isolated in low yield (2%). The inseparable isomeric 2:2 macrocycles **9**

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