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Structures of Lactones from the Acid-Catalyzed Cyclization of *exo*- and *endo*-Bicyclo[2.2.2]oct-5-ene-2-carboxylic Acids

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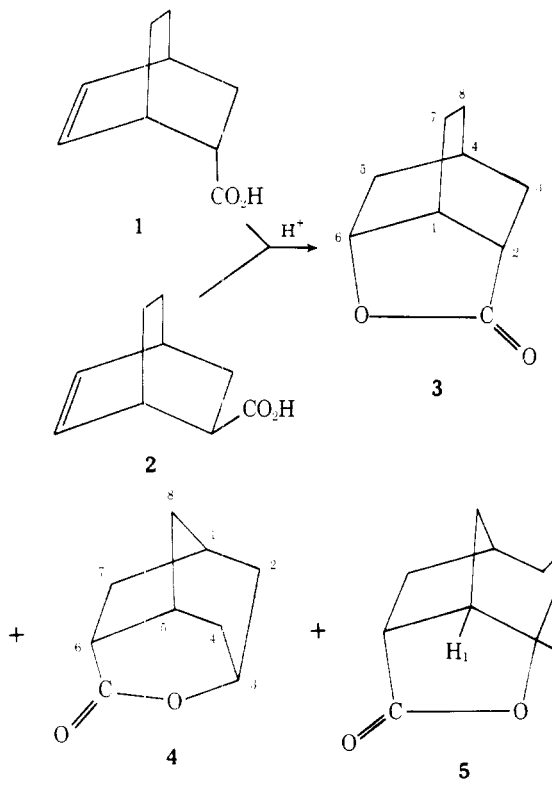
The structures of the γ- and δ-lactones obtained in the acid-catalyzed cyclization of bicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic acid have been established. By means of chemical degradation the lactones were proven to be 6-*endo*-hydroxybicyclo[2.2.2]octane-2-*endo*-carboxylic acid γ-lactone, 3(a)-hydroxybicyclo[3.2.1]octane-6-*endo*-carboxylic acid γ-lactone, and 2-hydroxybicyclo[3.2.1]octane-7-*endo*-carboxylic acid γ-lactone. The mechanism of these acid-catalyzed lactone formations was studied by means of deuterium incorporation. The [2.2.2]bicyclooctyl → [3.2.1]bicyclooctyl interconversion is discussed.

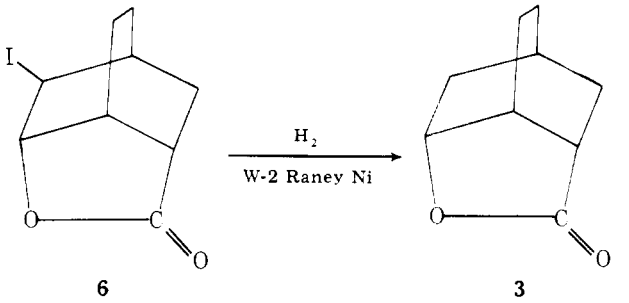
In the preceding paper we discussed the rearrangements which may occur upon acid-catalyzed intramolecular lactone formation in the *exo*- and *endo*-2-methylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acids.[1-3] Analogous cationic rearrangements also are observed in the bicyclo[2.2.2]octyl system.

Products from the acid-catalyzed lactonization of bicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic acid have been confused, and erroneous structures have been used in development of the concept of orbital steering.[4] Also, the structure of the iodo lactone has been incorrectly assigned.[5] We now present rigorous proof of structures in this series and also offer some mechanistic suggestions regarding the pathways involved in the rearrangement processes.

Acid-Catalyzed Cyclization of Endo Acid 1 and Exo Acid 2. Over a wide range of acid concentrations, the exo or endo acids yielded three lactones in varying amounts (Table I). No other products were detected. The lactones were partially separated by column chromatography, and final separation was accomplished by preparative thin-layer chromatography.



Proof of Structure of 6-*endo*-Hydroxybicyclo[2.2.2]octane-2-*endo*-carboxylic Acid γ-Lactone (3). γ-Lactone **3** was identified by comparison of its IR, NMR, and mass spectra obtained with those of an authentic sample which was prepared by hydrogenolysis of the iodo lactone of established structure,[6] namely, 5-*exo*-iodo-6-*endo*-hydroxybicyclo[2.2.2]octane-2-*endo*-carboxylic acid γ-lactone (**6**) over Raney nickel. A mixture melting point of the two



products showed no depression. Moreover, lactone **3** had the correct elemental analysis and a melting point identical with that reported.[6]

Proof of Structure of 3(a)-Hydroxybicyclo[3.2.1]-octane-6-*endo*-carboxylic Acid δ-Lactone (4). The IR spectrum of **4** showed an absorption of 1730 cm^{-1} (δ-lactone C=O).[7,8] The NMR spectrum contained a characteristic doublet of doublets ($J_{H2,H3}$ and $J_{H4,H3}$ = 2.5 Hz) at δ 4.6 assigned to the C_3 equatorial proton. The high-resolution mass spectrum showed a strong molecular ion at *m/e* 152 and a base peak at *m/e* 66. Important additional peaks derived from the parent ion appeared at *m/e* 134 (P − H_2O), 124 (P − CO), 108 (P − CO_2), and 80 (P − $C_3H_4O_2$). The peaks at *m/e* 66 and 80 probably correspond to retro-Diels–Alder fragmentations.[9] The base peak, *m/e* 66, agrees with formation of a cyclopentadiene fragment ion while the peak at *m/e* 80 may correspond to cycloelimination of acrylic acid ($C_3H_4O_2$) and production of a residual fragment ion of 1,3-cyclohexadiene. Since no conclusive structural assignment could be based on these data

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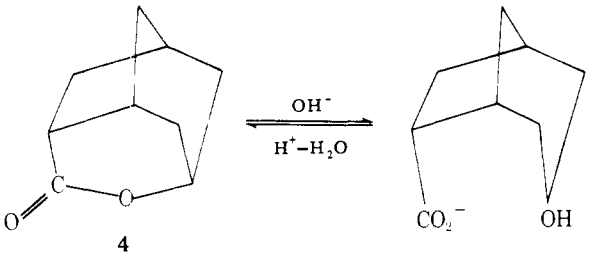
Table I. Product Distribution in the Acid-Catalyzed Cyclization of 1 and 2

reactant	conditions	time (h), temp (°C)	% yield	3/4/5
1	99.5% H_2SO_4	0.5, 0; 0.5, 25	88	3:5:0.05
2	99.5% H_2SO_4	0.5, 0; 0.5, 25	85	1:3:0.05
1	75% H_2SO_4	3.0, 0	90	1.1:1:0.05
2	75% H_2SO_4	3.0, 0	93	1:1.1:0.05
1	HCl/ether	24, 20	0	
2	HCl/ether	24, 20	0	
1	HOAc/H_2SO_4 (cat)	8, reflux	39	8:1:1
2	HOAc/H_2SO_4 (cat)	8, reflux	35	2.4:1:1
1	HOAc	24, reflux	0	
2	HOAc	24, reflux	0	

alone, a chemical degradation scheme was devised for definitive proof of structure.

Initially it was observed that 1 equiv of **4** was hydrolyzed



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by 1 equiv of sodium hydroxide. However, attempts to isolate the corresponding hydroxy acid by careful acidification were unsuccessful and only the starting lactone could be obtained.

This was not unexpected behavior since Brown et al.[10] have observed that various γ- and δ-hydroxy acids exist largely as the lactone at room temperature.

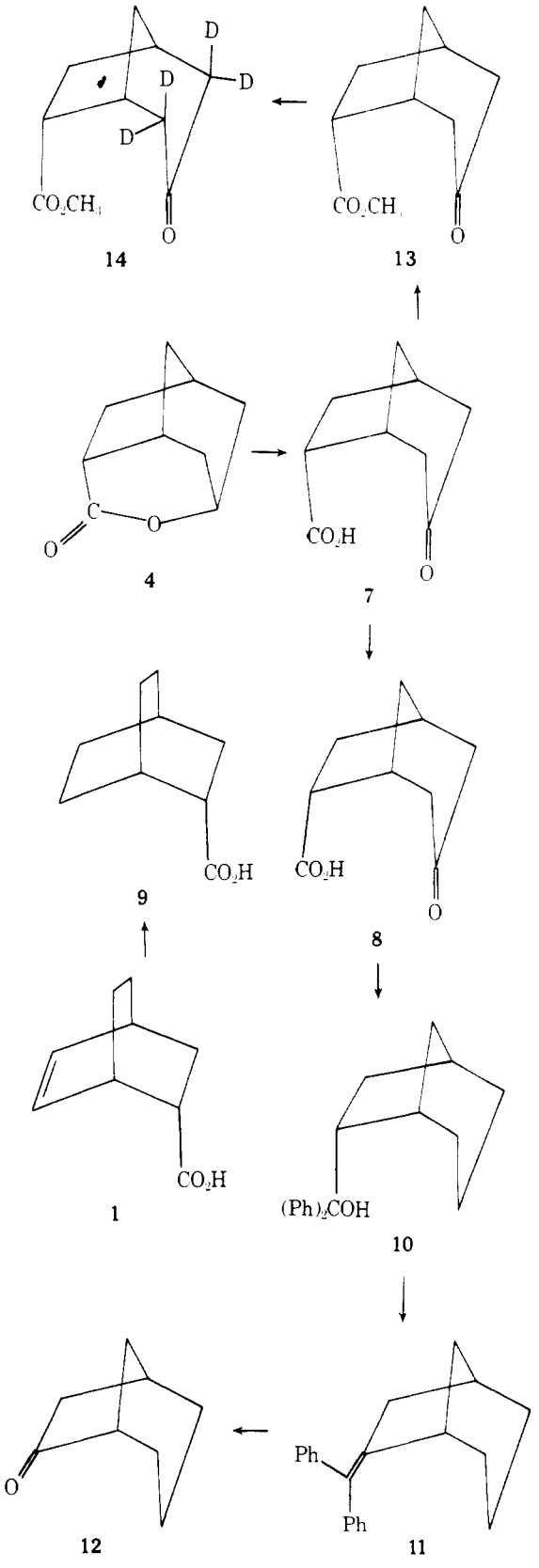
Since the hydroxy acid could not be isolated, an oxidation process under neutral or basic media was required. Scheme I summarizes the complete degradative process.

Oxidation of lactone **4** to the keto acid **7** was accomplished by two methods. In the usual procedure[11] basic potassium permanganate oxidation gave poor yields (<25%) of 3-oxobicyclo[3.2.1]octane-6-*endo*-carboxylic acid (**7**). However, a new oxidation method was used which has proven to be generally useful in the oxidation of lactones to the corresponding keto acids.[12] In this method the lactone was hydrolyzed with 1 equiv of base and then oxidized with ruthenium dioxide. This afforded an excellent yield (88%) of keto acid (**7**) (see Scheme I).

The IR spectrum of the product in chloroform showed broad absorptions at 1713 (C=O) and 3500 (acid O–H) cm^{-1}. However, in a Nujol dispersion two well-defined carbonyl absorptions appeared at 1740 (ketone C=O) and 1690 (acid C=O) cm^{-1}. The NMR spectrum was marked by the appearance of a downfield singlet at δ 7.0 for the acid proton. The product also gave the expected elemental analysis. Thioketal, mp 150–150.5 °C, and dinitrophenylhydrazone, 235–235.6 °C, derivatives were prepared, and both compounds gave the expected elemental analyses. The IR spectrum of the thioketal contained an absorption at 1700 cm^{-1} (acid C=O), and the NMR spectrum showed indicative resonances at δ 10.7, a singlet for the acid proton, and at δ 3.3, a triplet for the two thioketal methylenes ($-SCH_2CH_2S-$).

The ketone function of keto acid **7** was then reduced to methylene using the Huang-Minlon modification of the Wolff–Kishner reaction.[13] This procedure afforded an excellent yield (88%) of bicyclo[3.2.1]octane-6-*endo*-carboxylic acid (**8**) (see Scheme I). The IR spectrum of **8** showed absorptions for the carboxyl group at 3525 (acid O–H) and 1700 (acid C=O) cm^{-1}. Besides broad absorptions in the aliphatic region, the NMR spectrum contained a downfield singlet at δ 9.7 for the acid proton.

Scheme I. Degradative Reactions of δ-Lactone 4



At this point saturated acid **8** was compared to bicyclo[2.2.2]octane-2-carboxylic acid (**9**), which was prepared by hydrogenation of the unsaturated acid **1** (see Scheme I). Both compounds had close melting points; however, a mixture of the two showed a depressed melting point. The IR and NMR

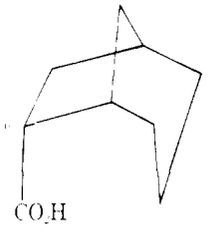
spectra of the two compounds were different. Since the two saturated acids were not identical, it was assumed and later proved, vide infra, that **8** had a rearranged bicyclo[3.2.1] skeleton.

The acid **8** was then treated with diazomethane to yield the methyl ester, which was not isolated but was treated with 2 equiv of phenylmagnesium bromide to produce 6-*endo*-(diphenylhydroxymethyl)bicyclo[3.2.1]octane (**10**). The IR spectrum of the alcohol showed absorptions at 3610 (free OH), 3030 (aromatic CH), and 1595 (aromatic C=C) cm^{-1}. The NMR spectrum contained a broad resonance centered at δ 7.5 for the aromatic protons and a triplet at δ 3.1 for the deshielded C_6 exo proton.

Alcohol **10** was then dehydrated with *p*-toluenesulfonic acid to yield (100%) 6-(diphenylmethylene)bicyclo[3.2.1]octane (**11**) (see Scheme I). The IR spectrum of the olefin displayed absorptions at 3025 (aromatic CH), 2940 (aliphatic CH), and 1595 (aromatic C=C) cm^{-1}.

Olefin **11** was then oxidized with ruthenium tetroxide in carbon tetrachloride at 0 °C (see Scheme I). The product was isolated by preparative TLC and purified by sublimation to yield the known[14] bicyclo[3.2.1]octan-6-one (**12**) in 40% yield. The IR spectrum of the ketone showed a carbonyl absorption at 1745 cm^{-1} in carbon tetrachloride and at 1725 cm^{-1} in chloroform. These data agreed with spectra previously reported for **11**.[8,15] Also, the mass spectrum of this volatile ketone was identical with the one described in the literature.[8] The semicarbazone derivative of **12** gave the expected melting point.[15] In addition to the above evidence for identification, TLC, IR, and GLC data for the product were identical with those of an authentic sample.[16]

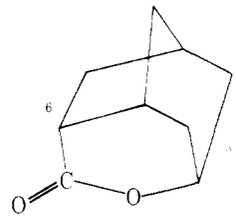
On the basis of this scheme, the carboxylic acid fragment of rearranged lactone **4** must be at the 6-endo position of the bicyclo[3.2.1]octane ring. The possibility that the carboxyl



group is in the 6-exo position is eliminated, a priori, by the fact that no δ-lactone is possible in this case. As shown below, the position of the alcohol oxygen requires the endo configuration for the C_6-carboxyl group.

To fix the oxygen locus of the δ-lactone, keto acid **7** was treated with diazomethane to yield methyl 3-oxobicyclo[3.2.1]octane-6-*endo*-carboxylate (**13**) (see Scheme I). The IR spectrum of the keto ester showed bands at 1730 (ester C=O) and 1710 (ketone C=O) cm^{-1}. The ketonic carbonyl band is at the same frequency as the ketone absorption reported for the bicyclo[3.2.1]octan-3-one.[17] The NMR spectrum showed a singlet δ 3.7 for the methyl group, while the mass spectrum of **13** showed a parent ion at *m/e* 182.

Compound **13** was then dissolved in deuteriomethanol containing a catalytic amount of sodium methoxide. After 24 h, methyl 2,2,4,4-tetradeuterio-3-oxobicyclo[3.2.1]octane-6-*endo*-carboxylate (**14**) was isolated. The NMR spectrum of **14** still showed the methyl signal at δ 3.7, but an average of five integrations indicated that the aliphatic region contained only seven protons. Also, the mass spectrum of **14** had a parent ion at *m/e* 186. Clearly, four deuterium atoms were incorporated into the molecule. The extent of isotopic exchange and the characteristic IR absorption placed the keto group on the 3 position of the bicyclo[3.2.1] skeleton. Therefore, the hydroxyl end of lactone **4** is situated at the 3-axial position and the lactone has a 3,6 juncture. The alternative δ-lactone would yield a keto group adjacent to the bridgehead which would exchange only three hydrogens for deuterium.



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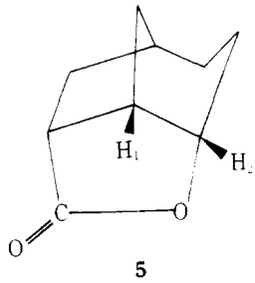
Proof of Structure of 2(e)-Hydroxybicyclo[3.2.1]-octane-7-*endo*-carboxylic Acid γ-Lactone (5). Lactone **5** was isolated in small yield (<5%) from the reaction of the unsaturated acid **1** and **2** (Table I). Final separation of this lactone from the crude mixture was difficult because **5** eluted from the column between the other lactone products. In fact, it was only isolated in pure form by preparative TLC.

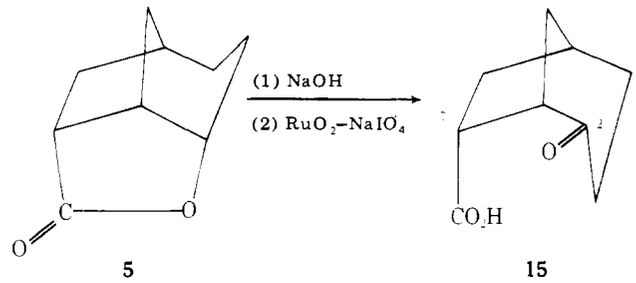
The IR spectrum of lactone **5** showed an indicative absorption at 1755 cm^{-1} (lactone C=O), characteristic of γ-lactones.[18] Since only one γ-lactone, namely, **3**, is possible with the bicyclo[2.2.2]octane skeleton, **5** must be a bicy-



5

clo[3.2.1]octyl lactone. The NMR spectrum exhibited one downfield signal at δ 5.0 which appeared as a doublet with a large coupling constant (J = 9.5 Hz). This coupling constant seems reasonable for a lactone with a structure such as **5**. In this structure the H_1 and H_2 protons would be expected to couple extensively because they become almost eclipsed when the cyclohexane ring assumes a boat conformation. Except for the peak intensities, the mass spectrum of **5** was *identical* with the mass spectrum of bicyclo[3.2.1]octyl γ-lactone **4**. This indicates the close similarity between the two lactones. The compound also gave the expected carbon and hydrogen analysis.

Obviously, based upon the foregoing results, the best chemical method for identification of this lactone would be degradation to the saturated acid **8** (see Scheme I). Toward this end, **5** was hydrolyzed with sodium hydroxide and oxidized with ruthenium tetroxide to yield (44%) 2-oxobicyclo[3.2.1]octane-7-*endo*-carboxylic acid (**15**). The IR



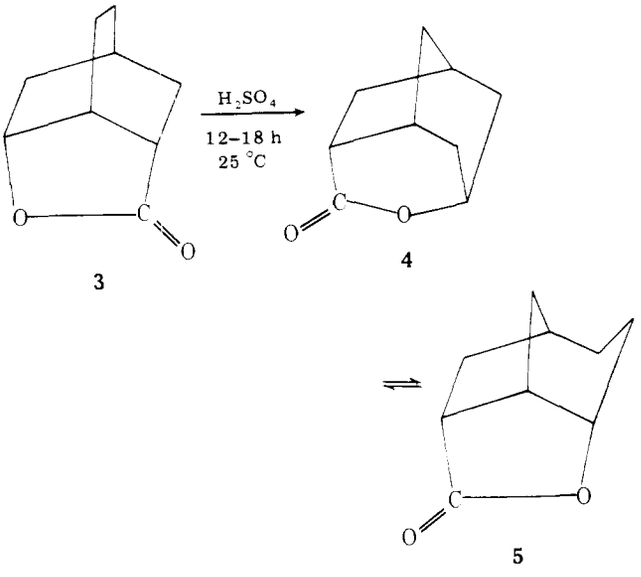
5 **15**

spectrum showed only one carbonyl absorption at 1710 cm^{-1} (C=O) and a broad band at 3500 cm^{-1} (acid O–H), and the spectrum was different from that of its isomer **7**. To prove that **15** contained two carbonyl functions it was treated with diazomethane. The resulting methyl ester gave an IR spectrum with two carbonyl bands at 1735 (ester C=O) and 1715 (ke-

tone C=O) cm^{-1}. This latter ketonic absorption coincides with the one reported for a substituted bicyclo[3.2.1]octan-2-one.[19] Based on this fact the ketone function of **15** was assigned to the C_2 position, and consequently the hydroxyl fragment of lactone **5** was assigned to the C_2 equatorial position.

When keto acid **5** was reduced using the Wolff-Kishner method a mixture (<25%) resulted. All efforts to separate and purify the products failed. However, it seems that of all possible bicyclo[3.2.1] γ-lactones, the 2,7-lactone structure fits best with the data obtained.

Equilibration of Lactones in Acid Medium. To assure that the lactone products were not interconvertible under reaction conditions (0–3 h), each lactone was investigated for possible rearrangement in the strongest possible acid medium (99.5% H_2SO_4). TLC was used to follow the reactions of each lactone, and the relative peak areas of the characteristic downfield protons in the NMR spectrum gave an approximate ratio for the products formed. After 3 h no equilibration was observed.[3] Only after 12 h had about 90% of lactone **3** rearranged to **4.** After 24 h **3** could not be detected by either TLC or NMR. However, during this time period (12–24 h) TLC showed that lactone **3** isomerized to **5.** The amount of **5**



3 4

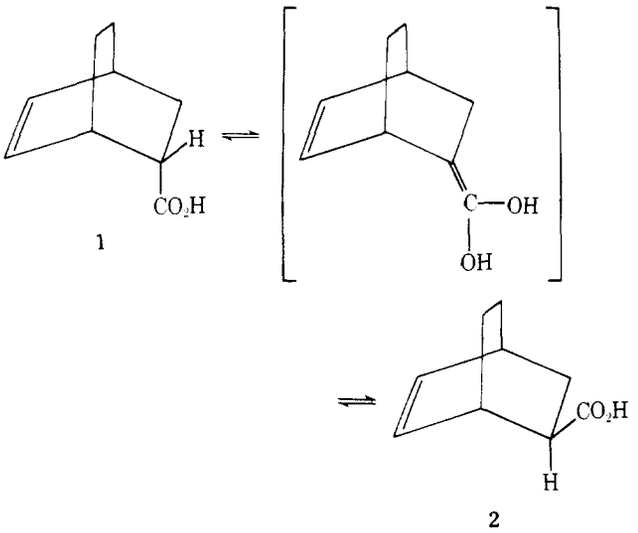
5

steadily increased over 5 days, at which time it comprised about 45% of the mixture. Extensive decomposition also occurred during this period, and accurate yields of **4** and **5** could not be determined. On the other hand, when a small amount of **5** was treated with acid for 2 h, lactone **4** was detected by TLC. It is clear that these two bicyclo[3.2.1]octyl lactones are readily interconvertible, but an equilibrium situation could not be detected because of the concomitant decomposition.

From these results, it is apparent that the cyclization reactions having short reaction times (0–3 h) *are not complicated* by product interconversions which are *slower* processes. Also, the above data indicate that lactone **3** is thermodynamically the least stable of the products formed.

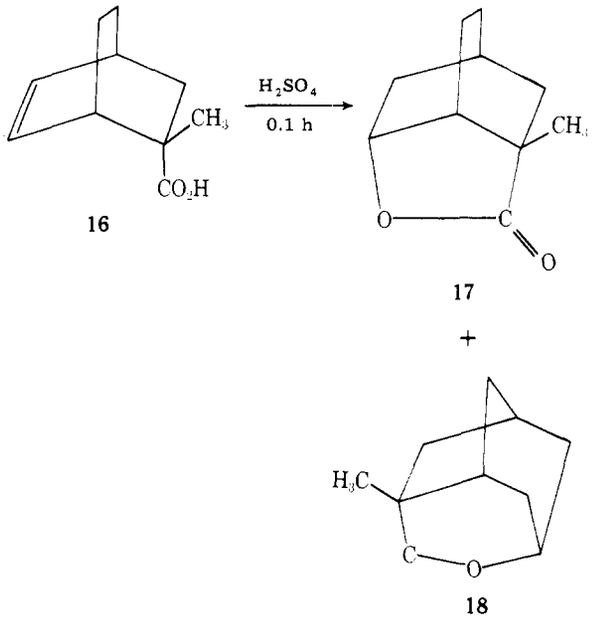
Isomerization of Starting Materials. The possibility that the starting materials, **1** and **2,** were interconverting by enolate formation before cyclization was tested by reacting 2-*exo*-methylbicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic acid (**16**) under the same conditions. Since **16** has no α hydrogen, isomerization of the type shown is impossible. Therefore, **16** should give approximately the same yields of γ- and δ-lactones as the unsubstituted acids, if isomerization is unimportant.

When 2-*exo*-methybicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic acid (**16**) was treated with concentrated sulfuric acid, two lactones were isolated by column chromatography. The



1 2

one in smaller yield had spectral and physical properties identical with those of an authentic sample of 2-*exo*-methyl-6-*endo*-carboxylic acid γ-lactone (**17**).[20] The major product, 6-*exo*-methyl-3(a)-hydroxybicyclo[3.2.1]octane-6-*endo*-carboxylic acid δ-lactone (**18**), was assigned on the basis

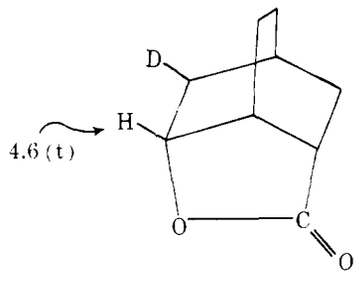


16 17 18

of spectral data, which were similar to those of lactone **4.** The IR spectrum contained a δ-lactone carbonyl absorption at 1730 cm^{-1} (C=O), and the NMR spectrum showed a downfield signal at δ 4.6 for the C_3 equatorial proton and a singlet at δ 1.2 for the methyl protons. Also, the spectrum gave the correct integration ratio.

Although a somewhat higher yield of the rearranged lactone was obtained for the methyl-substituted lactone, the overall reaction course followed by acids **1** and **16** is identical, and this may be taken to indicate that starting material isomerization is not significant.

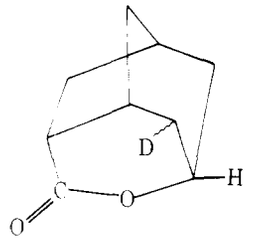
Catalyzed Cyclizations in Deuterated Acids. To investigate the stereochemistry of proton addition to these unsaturated acids, **1** was treated with deuteriosulfuric acid. The minor product, a deuterated lactone, had the same melting point as **3.** However, in this case (**3**-d_1) the NMR spectrum showed a broad downfield triplet at δ 4.8 (J = 2.0 Hz) for the C_6 exo proton of **3.** The mass spectrum of **3**-d_1 showed a parent peak at m/e 153 and a base peak at m/e 80. Compared to the mass spectrum of lactone **3** (parent ion at m/e 152 and a base ion at m/e 79), it is apparent that *one deuterium* is present in **3**-d_1. Based on previous deuteration studies[21] and on the



3-d_1

change in coupling for the C_6 exo proton (broad multiplet in **3**, a triplet in 3-d_1), the deuterium is assigned to the 5-exo position.

The major product, 4-d_1, had the same melting point as **4**. The NMR spectrum of the compound contained a downfield



4-d_1

signal at δ 4.6 for the C_3 equatorial proton. The signal appeared as a broad singlet with a half-height width of 6 Hz and was quite different from the appearance of the C_3 proton in the undeuterated material **4**. Based on this difference, the deuterium was assigned to the C_4 position adjacent to the C_3 proton. Mass spectral evidence supported this assignment. The mass spectrum of 4-d_1 showed a parent ion peak at *m/e* 153 (**4** exhibited a parent at *m/e* 152) and a base peak at *m/e* 66. As noted before, the base ion probably corresponds to a cyclopentadiene fragment. Since undeuterated lactone **4** gives the same base peak, it is assumed that deuterium is not incorporated into the cyclopentane portion of the bicyclo[3.2.1] skeleton. The fact that 4-d_1 exhibits a strong fragment peak at *m/e* 81 [deuterated cyclohexadiene fragment, $(C_6H_7D)^+\cdot$] while **4** shows a fragment ion at *m/e* 80 [$(C_6H_8)^+\cdot$] is additional evidence that deuterium is in the cyclohexane portion of the bicyclooctane ring.

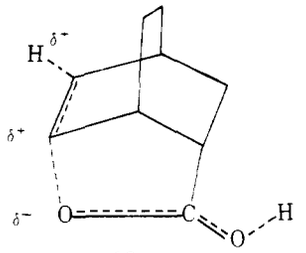
Discussion

As summarized in Table I, the acid-catalyzed reaction of endo acid **1** produced compounds resulting from neighboring group interaction (a bicyclo[2.2.2]octyl lactone) and rearrangement (bicyclo[3.2.1]octyl lactones).

The possibility that the endo acid **1** isomerized to the exo acid **2** before reaction was excluded on the basis of an α-substitution experiment in which the α hydrogen of **1** was replaced by a methyl group. The acid-catalyzed reaction gave a γ- and a δ-lactone. With the exception of the α-methyl group, these products were identical in structure with those formed from the unsubstituted endo acid **1**. Therefore, we conclude that the endo acid does not isomerize before cyclization occurs.

When the endo acid **1** is refluxed in HOAc containing a catalytic amount of H_2SO_4 for 8 h (Table I), 80% of the product isolated was bicyclo[2.2.2]octyl γ-lactone **3**. Compared to conditions of 99.5% H_2SO_4 or to the reactions of the exo acid **2** (Table I), this reaction produced the highest yield of **3**. Since this lactone converts irreversibly to bicyclo[3.2.1]octyl δ-lactone **4**, it is apparent that the HOAc reaction is yielding the product **3** of kinetic control.

The mechanism for formation of **3** in acetic acid is possibly an anti addition of the HOAc mechanism involving neighboring group interaction. This pathway is similar to the one proposed by Fahey[22,23] for the acid-catalyzed addition of acetic acid to cyclohexene. A number of observations support this mechanism. First, neighboring group interaction may be important in the formation of **3** because endo acid **1** gives a higher percentage of **3** than does exo acid **2**. Second, when *endo*-**1** is cyclized with deuterated acids, a deuterated lactone **3**-d_1 results with the isotopic label at the C_5 exo position. Clearly, anti addition is occurring. Third, in stronger acids (99.5% H_2SO_4) rearranged lactones predominate, probably forming via carbonium ion intermediates. Under these conditions a transition state such as **19** could account for all of the above observations.

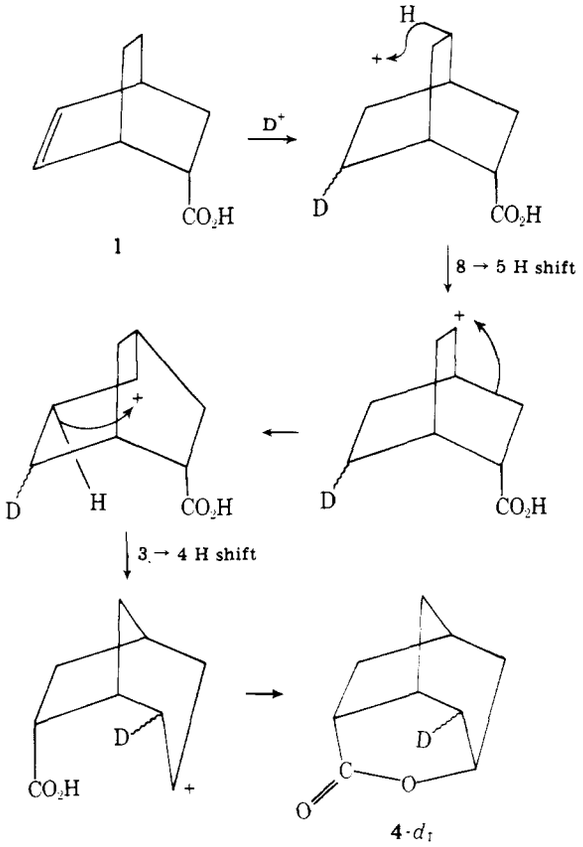


19

When the endo acid **1** is lactonized under stronger acid conditions, the percentage of rearranged lactone **4** increased to a point where in 99.5% H_2SO_4 **4** comprises about 67% of the mixture. Because of short reaction times (<1 h), product interconversion is negligible. Under these conditions rearrangement competes favorably with the anti-addition reaction mentioned above.

In light of the strong protonating ability of the solvent (H_2SO_4) and the extensive rearrangements it seems that carbonium ion intermediates are present in strong acid media. To investigate which cationic modes of rearrangement compete with anti addition, acid **1** was cyclized in deuteriosulfuric acid. The rearranged lactone **4** contained one deuterium atom. The mechanism presented in Scheme II involves a transan-

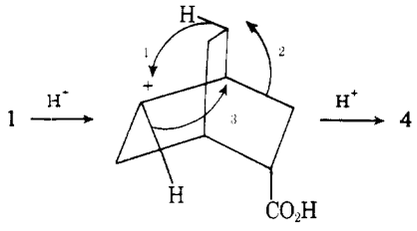
Scheme II. Mechanism for Formation of Lactone 4



4-d_1

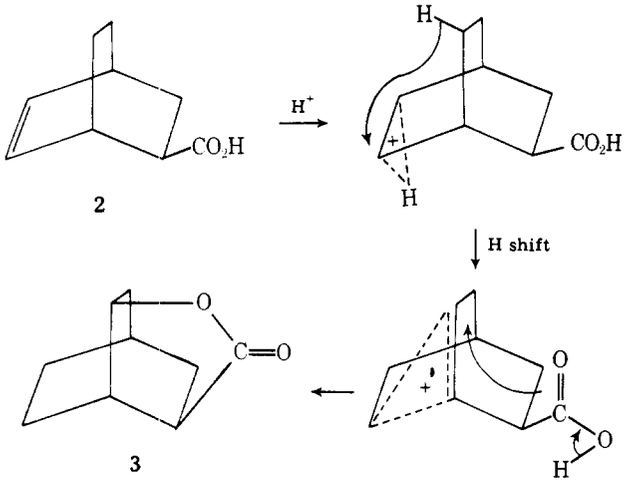
nular hydride shift ($C_8 \rightarrow C_5$), a carbon–carbon δ-bond shift, another hydride shift ($C_3 \rightarrow C_4$), and subsequent lactonization. This pathway is similar to the one advanced by Beckmann[24] for lactonization observed in the norbornyl ring system. The transannular hydride shift in the bicyclooctane series has been extensively studied.[25] However, in a recent investigation affecting the interpretation of these results, Kwart and Irvine[26] have related the tendency for a hydride shift to the acidity of the medium. In the acetolysis of bicyclo[2.2.2]sulfonium salts the amount of product formed via a pathway involving 2,7-transannular hydride migration increases as the acidity of the medium increases. Assuming the validity of the mechanism presented above for the formation of **1**, a similar trend is observed in these lactonizations.

We propose that in strong acid a rearrangement pathway predominates in which a bicyclo[2.2.2]octene carboxylic acid is converted to a bicyclo[3.2.1]octane lactone (**4**) via a series of backside shifts of hydrogen and carbon.



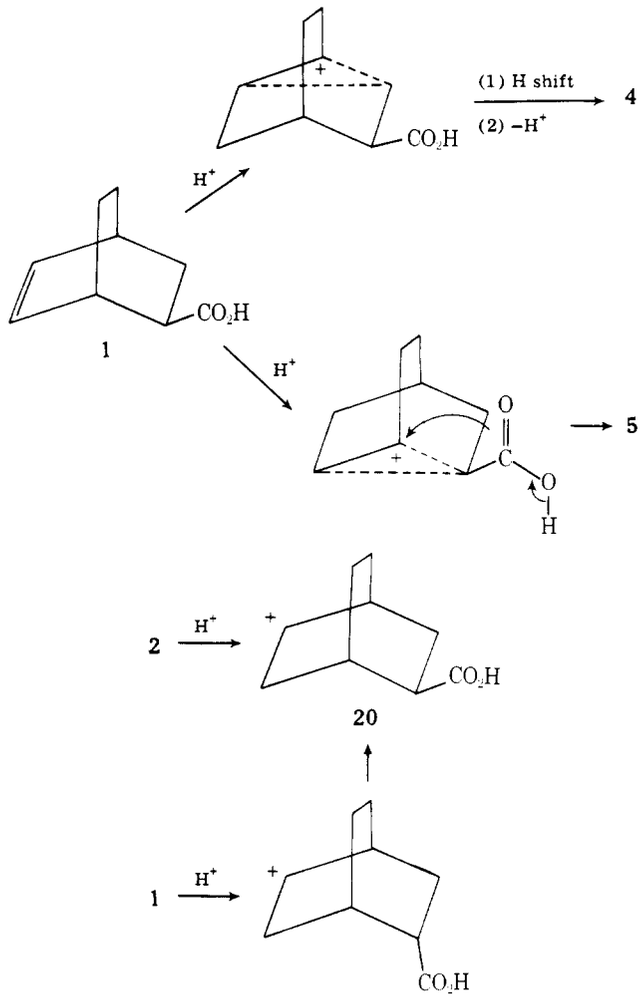
If the exo acid **2** is exposed to the acetic acid–sulfuric acid catalyzed condition, three lactones were detected. Since the isomerization of the carboxylic acid group is improbable, the products cannot be derived from simple anti addition. Also the lack of any syn-addition products indicates that all three lactones are products of rearrangement transformations.

The major product (50%) is γ-lactone **3**, which can be pictured as forming via a transannular 7 → 6 hydride shift.



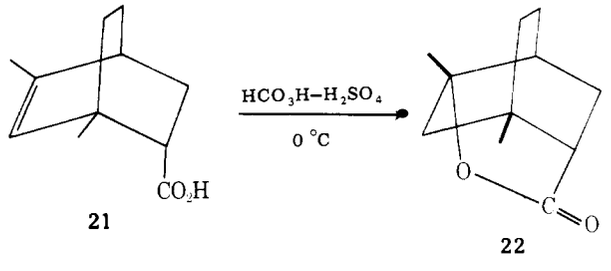
The formation of lactones **4** and **5** (50%) can be envisioned as arising via initial Wagner–Meerwein shifts. In one case, δ-lactone **4** may arise via initial C_3–C_4 bond migration in the protonated acid while the γ-lactone **5** may be formed by a similar C_1–C_2 bond migration.

As the protonating power of the solution is increased, the exo acid yields two lactones, **3** and **4**. Because both the exo and endo acids give the same products in about the same yield, it seems that a common intermediate may be involved in these reactions. Since the protonated endo acid can be converted to the protonated exo acid by a transannular hydride shift, it is proposed that a carbonium such as **20** is formed from **2** and **1**. This ion undergoes a subsequent carbon–carbon σ-bond shift and eventually cyclizes to give the observed δ-lactone **4**. In a similar fashion a common intermediate like **20** could be

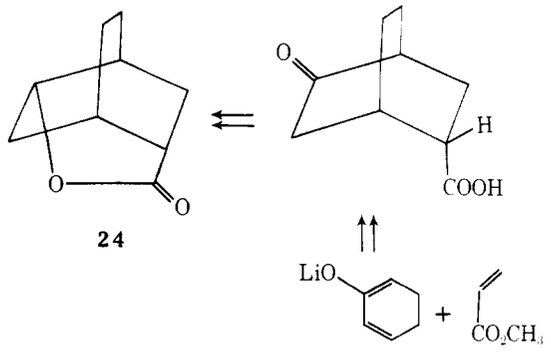


formed by a transannular hydride shift in strong acid and lead to δ-lactone **3**.

Some relevant work in this series has been reported[27] by Mirrington and Schmalzl. They found that the acid-catalyzed lactonization of the dimethyl-substituted bicyclo[2.2.2]octenecarboxylic acid (**21**) produced a bicyclo[2.2.2]octyl δ-lactone (**22**). The structure assignment was based on NMR



and IR evidence and the supposition that the factor governing δ-lactone formation was generation of a stable tertiary carbonium ion at C_5.



Finally, part of the reason for our work was to prove that the δ-lactones in this series were not a bicyclo[2.2.2]octyl structure (**24**) as mistakenly reported by Storm and Koshland.[4]

This lactone has now been synthesized by Lee[28] using the above route and has mp 204.5–205.5 °C and IR 1750 cm^{-1}. The relatively high carbonyl stretching frequency may be due to ring strain in this system.

Experimental Section

Preparation of Bicyclo[2.2.2]oct-5-ene-2-carboxylic Acids (1 and 2). A mixture of **1** and **2** was prepared on a 190-g scale according to the procedure of Boehme et al.[5] However, improved yields (80–83%) of the acids (102 °C, 1.15 mm) were obtained if equimolar amounts of acrylic acid and 1,3-cyclohexadiene were heated in a sealed Clausius tube at 155 °C for 17 h with a catalytic amount of hydroquinone present.

5-*exo*-Iodo-6-*endo*-hydroxybicyclo[2.2.2]octane-2-*endo*-carboxylic Acid γ-Lactone (6) and Bicyclo[2.2.2]oct-5-ene-2-*exo*-carboxylic Acid (2). A mixture of **1** and **2** (125 g, 0.82 mol) was treated with a basic iodine solution according to the procedure of Boehme. The reaction mixture was extracted with four portions of ether. The organic extracts were combined, washed twice with sodium hydrogen sulfite solution, and dried. The solvent was removed in vacuo to give a yellowish solid (131 g) which was crystallized from acetone–hexane to yield 129 g (56%) of iodo lactone **6**: mp 80–81 °C (lit.[6] 80–81 °C); IR ($CHCl_3$) 1785 (lactone C=O) and 645 (C–I) cm^{-1}; NMR ($CDCl_3$) δ 5.02 (d, 1, J = 6 Hz, $C_{6\text{-exo}}$-H), 4.40 (d, 1, J = 3 Hz, $C_{5\text{-endo}}$-H), and 2.70–1.40 (broad m, 9).

The reaction mixture was acidified and extracted with three portions of ether. The extracts were combined and dried, and the solution was concentrated to yield a red semisolid which was vacuum distilled twice to produce 39.5 g (32%) of acid **2**: mp 46–48 °C (lit.[5] 46–48 °C); IR ($CHCl_3$) 3520 (acid O–H), 1700 (acid C=O), and 695 (alkene CH) cm^{-1}; NMR ($CDCl_3$) δ 10.14 (s, 1, >COOH), 6.30 (t, 2, J = 4 Hz, =CH), 2.87 (broad m, 1, >CHCOOH), and 2.70–1.00 (broad m, 8).

Bicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic Acid (1). The iodo lactone **6** (100 g, 0.36 mol) was dissolved in glacial acetic acid (400 mL), and activated zinc (100 g) was added. The heterogeneous mixture was stirred mechanically for 1.5 h at 15 °C. The white solid which formed during reaction was filtered, and the filtrate was diluted with a sixfold excess of water. The solution was extracted with three portions of ether. The extracts were combined and dried, and the solvent was removed in vacuo to yield a yellow oil. The oil was vacuum distilled (108 °C, 0.8 mm), and 48.1 g (88.5%) of a clear solid was obtained: mp 55–56.5 °C (lit.[5] 56–56.6 °C); IR ($CHCl_3$) 3520 (acid OH), 1700 (acid C=O), and 695 (alkene CH) cm^{-1}; NMR ($CDCl_3$) δ 10.55 (s, 1, COOH), 6.40 (m, 2, =CH), and 3.20–1.10 (9).

Acid-Catalyzed Cyclization of 1 and 2. Lactone Formation in Strong Acids. In a typical reaction either **1** or **2** (1.0 g, 6.6 mmol) was treated with concentrated sulfuric acid (99.5%) at 0 °C for 0.5 h and at 25 °C for 0.25 h. The resulting yellow solution was carefully poured onto a tenfold excess of ice. A white precipitate formed, and the mixture was extracted with five portions of ether or chloroform. The organic extracts were combined, washed with saturated sodium bicarbonate solution, and dried. The solvent was removed in vacuo to yield a yellowish solid which gave two peaks upon GLC (25% SE-30, 270 °C) and three components upon TLC (70% ether–hexane). Optimum conditions for separation were attained by chromatography on silica gel (100 g, 60 × 2.5 cm) with 10% ether–petroleum ether as the eluant (see Table II). Although different eluants (benzene–hexane or ether–hexane) could be used, fractions containing a mixture were obtained and final separation was accomplished by preparative TLC (75% ether–hexane). Yields are recorded in Table III.

Lactone Formation in Weak Acids. Either **1** or **2** (0.50 g, 3.29 mmol) was dissolved in glacial acetic acid (5 mL) containing a catalytic amount of sulfuric acid (0.15 mL). The solution was refluxed for 8 h and then cooled to 25 °C. The mixture was poured onto an ice solution (30 mL) containing sodium bicarbonate (8.4 g). The basic solution was extracted with three portions of ethyl acetate. The extracts were combined and dried, and the solvent was removed in vacuo to yield a semisolid. The material showed three components on TLC (60% ether–hexane) which were identical with products formed under strong acid conditions. The mixture was separated by chromatography on silica gel (40 g, 50 × 1.5 cm) with 10% ether–hexane as the eluant (Table III).

6-*endo*-Hydroxybicyclo[2.2.2]octane-2-*endo*-carboxylic Acid γ-Lactone (3). Lactone **3** was purified by repeated crystallization from hexane or acetone–hexane to yield white needles: mp 205–206 °C (lit.[6] 205–206 °C); IR ($CHCl_3$) 1760 cm^{-1} (lactone C=O); NMR ($CDCl_3$) δ 4.67 (m, 1, $C_{6\text{-exo}}$-H), 2.55 (m, 2), and 2.0–1.40 (broad m, 9); mass spectrum, parent m/e 152, base m/e 79, m/e 134 (P − H_2O), 124 (P − CO), 108 (P − CO_2), 96, 80, 67, and 66.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.05; H, 7.90. Found: C, 70.99; H, 7.90.

The TLC and IR, NMR, and mass spectral results of **3** were identical with those recorded for the product obtained from the hydrogenolysis of **6**, and the melting point was not depressed for a mixture of the two samples.

3(a)-Hydroxybicyclo[3.2.1]octane-6-*endo*-carboxylic Acid γ-Lactone (4). Lactone **4** was purified by repeated crystallization in acetone–pentane and by sublimation (106 °C, 0.43 mm) to yield a white solid: mp 239–241 °C (1 week at 25 °C, mp 233–235 °C); IR ($CHCl_3$) 1730 cm^{-1} (lactone C=O); NMR ($CDCl_3$) δ 4.60 (q, 1, 50-Hz sweep, half-height width = 8.5 Hz, C_3-H), and 3.20–1.60 (broad m, 11); mass spectrum, parent m/e 152, base m/e 66, m/e 134 (P − H_2O), 124 (P − CO), 96, 80, 79, and 67.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.05; H, 7.90. Found: C, 70.84; H, 7.77.

Compound **4** was hydrolyzed with 0.10 N sodium hydroxide solution, and 1 equiv of base was consumed per equiv of **4**.

2-Hydroxybicyclo[3.2.1]octane-7-*endo*-carboxylic Acid γ-Lactone (5). Lactone **5** was separated from the mixture by preparative TLC (75% ether–hexane). The solid obtained was sublimed (90 °C, 0.5 mm) and crystallized in hexane to produce a white solid: mp 173–176 °C; IR ($CHCl_3$) 1755 cm^{-1} (lactone C=O); NMR ($CDCl_3$) δ 4.97 (d, 1, J = 9.5 Hz, 50-Hz sweep, C_2-H), and 3.33–1.10 (broad m, 11); mass spectrum, parent m/e 152, base m/e 79, m/e 134 (P − H_2O), 124 (P − CO), 108 (P − CO_2), 96, 80, 76, and 67.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.05; H, 7.90. Found: C, 71.13; H, 7.98.

Preparation of an Authentic Sample of 3. Iodo lactone **6** (5.12 g, 0.018 mol) was dissolved in absolute ethanol (175 mL) and placed in a hydrogenation flask containing pyridine (5 g) and W-2 Raney nickel (15 g). The solution was shaken mechanically for 24 h under hydrogen atmosphere (30 psi). The heterogeneous solution was filtered, and the ethanol was removed in vacuo. The remaining green residue was dissolved in ether, and the solution was washed with water. The organic layer was dried, and the solvent was removed to yield 2.35 g of yellowish solid. The material was crystallized from ether–pentane to yield 1.86 g (67%) of a white solid (**3**), mp 205–206 °C (lit.[6] 205–206 °C). The melting point was not depressed for a mixture of this material and **3** obtained above. Also, spectral data for this compound were identical with those recorded for **3** which was obtained from the acid-catalyzed cyclizations.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.05; H, 7.90. Found: C, 70.99; H, 7.90.

Chemical Degradation of Lactone 4. (1) Bicyclo[3.2.1]octan-3-one-6-*endo*-carboxylic Acid (7). The lactone **4** was oxidized by two methods. One method involved treatment of **4** (5.0 g) with basic

Table II. Chromatography of Acid Catalysis Products from 1 and 2

fraction (25 mL)	product, mg
1–6	147 (mp 205–206 °C)
7–11	265 (mixture of three compounds)
12–25	349 (mp 239–241 °C)

Table III. Product Composition from Acid-Catalyzed Cyclization of 1 and 2

reactant	conditions	time (h), temp (°C)	% yield	% 3	% 4	% 5
1	99.5% H_2SO_4	0.5, 0; 0.25, 25	85	21	64	<1
2			88	33	55	<1
1	75% H_2SO_4	5, 0	93	43	49	<1
2			90	47	42	<1
1	HCl/ether	24, 20	0			
2			0			
1	HOAc/H_2SO_4	8, reflux	35	17	7	10
2	(cat)		39	31	4	4
1	HOAc	24, reflux	0			
2			0			

potassium permanganate solution according to a procedure by Beckmann.[24] This method afforded 5.17 g of a crude solid which gave two spots on TLC (ether). One spot corresponded to unreacted lactone 4. The mixture was chromatographed on silica gel (100 g, 70 × 2.5 cm), and 2.94 g of lactone 4 was isolated from 25–75% ether–petroleum ether fractions while 1.67 g (25%) of a second component, 7, was isolated from 5–50% acetone–ether fractions, mp 179–180 °C.

Due to the relatively low yield of 7, a new procedure using ruthenium tetroxide was developed.[12] In this method 4.0 g (0.026 mol) of 4 was dissolved in a solution (100 mL) containing an equivalent amount of sodium hydroxide (52.8 mL of a 0.498 N solution). When the solution became homogeneous (0.25 h, 80 °C), it was cooled and found to be neutral to phenolphthalein indicator. The solution was stirred at 20 °C while a catalytic amount of insoluble ruthenium dioxide (40 mg, K & K Co.) was added. A solution (50 mg) of sodium metaperiodate (5.63 g, 0.027 mol) was added slowly to the stirred solution over a 2-h period. During each periodate addition the ruthenium dioxide dissolved and the yellow color of ruthenium tetroxide appeared. Reappearance of the black insoluble dioxide occurred within minutes, indicating consumption of the periodate in oxidation. After addition of the periodate, isopropyl alcohol (0.5 mL) was added and the solution was stirred for an additional 5 min. The solution was acidified with a 10% hydrochloric acid solution and then extracted with five portions of ethyl acetate. The organic extracts were combined and dried, and the solvent was removed in vacuo to yield 3.95 g of a crude solid. The material was crystallized from acetone or chloroform to produce 3.88 g (88%) of keto acid 7: mp 179–180 °C; IR ($CHCl_3$) 3500 (acid OH) and 1713 (acid C=O and ketone C=O) cm^{-1}; IR (Nujol) 1740 (ketone C=O) and 1688 (acid C=O) cm^{-1}; NMR (polysol-*d*) δ 7.0 (s, 1, COOH) and 3.10–1.70 (m, 11).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.30; H, 7.15. Found: C, 64.39; H, 7.24.

The dinitrophenylhydrazone derivative was prepared according to a known procedure.[29] The red material which formed was crystallized from 95% ethanol to yield red needles, mp 235–236.5 °C.

Anal. Calcd for $C_{15}H_{16}N_4O_6$: C, 51.70; H, 4.66. Found: C, 51.80; H, 4.79.

The thioketal derivative was prepared by dissolving 7 (0.8 g, 4.75 mmol) in ethanedithiol (4.0 mL) and adding freshly distilled boron trifluoride etherate (1.5 mL) at 25 °C. The solution was diluted with water (50 mL) and extracted with three portions of ether. The extracts were combined and dried, and the solvent was removed in vacuo to yield a red oil. The oil was chromatographed over silica gel (40 g, 45 × 2 cm), and 0.77 g (66%) of a solid was isolated from the 25% ether–hexane fractions. The solid was crystallized from acetone–pentane to yield a white material: mp 150–150.5 °C; IR ($CHCl_3$) 3500 (acid OH) and 1700 (acid C=O) cm^{-1}; NMR (CDCl) δ 10.70 (s, 1, COOH), 3.32 (t, 4, J = 3 Hz, $-SCH_2CH_2S-$), and 3.20–1.55 (broad m, 11).

Anal. Calcd for $C_{11}H_{16}O_2S_2$: C, 54.10; H, 6.52. Found: C, 54.28; H, 6.61.

(2) Bicyclo[3.2.1]octane-6-*endo*-carboxylic Acid (8). Compound 7 was reduced using a modification of the Wolff–Kishner reaction.[13] In this way 7 (3.4 g, 0.02 mol) afforded 2.7 g (88%) of a waxy solid after hexane extraction. The solid was crystallized in ethanol–water and sublimed (55 °C, 0.4 mm) twice to yield 8: IR ($CHCl_3$) 3525 (acid OH) and 1700 (acid C=O) cm^{-1}; NMR ($CDCl_3$) δ 9.61 (s, 1, COOH) and 2.9–1.2 (broad m, 13).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.01; H, 9.10. Found: C, 69.74; H, 9.24.

The ester derivative of 8 was prepared by treatment of 8 (1.2 g, 7.8 mmol) in ether with a freshly prepared ether solution of diazomethane. This afforded 1.26 g (97%) of a yellow oil which gave a single spot on TLC (10% ether–pentane): IR ($CHCl_3$) 1730 cm^{-1} (ester C=O).

A sample of bicyclo[2.2.2]octane-2-carboxylic acid (9), mp 84 °C (lit.[30] 83–84 °C), prepared by hydrogenation of 1 over 5% palladium–charcoal (30 psi) when mixed with 8 gave a melting point depression, mp 64–68 °C.

6-*endo*-(Diphenylhydroxymethyl)bicyclo[3.2.1]octane (10). The methyl ester of 8 (1.25 g, 7.4 mmol) in ether (50 mL) at 0 °C was treated with a freshly prepared ethereal solution of phenylmagnesium bromide (25 mL of 0.6 M) according to a known procedure.[31] This afforded 2.17 g of a yellow oil which showed two spots on TLC (10% ether–hexane), one of which corresponded to the reactant ester. The mixture was chromatographed on silica gel (100 g, 70 × 2.5 cm), and 0.29 g (23%) of the ester was isolated from 20% benzene–pentane fractions while 1.48 g (70%) of 10 was isolated from 50% benzene–pentane fractions. IR ($CHCl_3$) 3610 (OH), 3030 (aromatic CH), and 1595 (aromatic C=C) cm^{-1}; NMR ($CDCl_3$) δ 7.65–7.05 (m, 10, aromatic H), 3.12 (t, 1, J = 7.5 Hz), and 2.4–1.1 (broad m, 13).

A sample of 10 was used for succeeding reactions without further purification.

6-(Diphenylmethylene)bicyclo[3.2.1]octane (11). Compound 10 (0.55 g, 1.7 mmol) was dissolved in benzene (50 mL) containing *p*-toluenesulfonic acid hydrate (0.075 g) and anhydrous calcium chloride (0.2 g).[32] The heterogeneous mixture was kept at reflux for 1.5 h, cooled, and filtered. The filtrate was washed twice with saturated sodium bicarbonate solution and then with water. The solution was dried, and the solvent was removed in vacuo to yield a yellow solid. The crude material was crystallized from acetone, and 0.52 g (100%) of white needles was obtained: mp 105–106 °C; IR ($CHCl_3$) 3025 (aromatic CH), 2940 (aliphatic CH), 1595 (aromatic C=C), and 700 (aromatic CH) cm^{-1}; NMR (CCl_4) δ 7.19 (broad m, 10, aromatic H), and 3.0–1.40 (broad m, 12).

Anal. Calcd for $C_{21}H_{22}$: C, 91.97; H, 8.03. Found: C, 91.74; H, 8.07.

Bicyclo[3.2.1]octan-6-one (12). A catalytic amount of ruthenium dioxide (10 mg) was added to carbon tetrachloride (15 mL), and the heterogeneous mixture was stirred vigorously while a solution of sodium metaperiodate (0.35 g, 1.6 mmol) was added at 10–15 °C. To the resulting yellow solution was added a solution of alkene 11 (0.12 g, 0.44 mmol) in carbon tetrachloride (5 mL). The black dioxide reappeared immediately, and the solution was stirred for 1.5 h at 20 °C. The two layers were separated, and the aqueous layer was extracted with two portions of ether. The organic solutions were combined and dried, and the solvent was removed in vacuo to yield a brownish oil (75 mg). TLC (7% ether–pentane) of the material indicated the presence of two compounds, one corresponding to benzophenone. Preparative TLC (7% ether–pentane) was used to separate the second component, which was then purified by three sublimations (25 °C, 10 mm) to yield 22 mg (40%) of a volatile waxy solid: mp 153–155 °C (lit.[14] 155–157 °C); IR (CCl_4) 1745 cm^{-1} (C=O) (lit.[8] 1745 cm^{-1}); IR ($CHCl_3$) 1725 cm^{-1} (C=O) (lit.[15] 1726 cm^{-1}); mass spectrum, parent *m/e* 124 and *m/e* 81, 80, 67, 54, and 41 (lit.[8] parent *m/e* 124 and *m/e* 81, 80, 67, 54, and 41).

The semicarbazone derivative was prepared and crystallized three times from benzene–pentane to yield needles, mp 180–182 °C (lit.[15] 187–190 °C).

TLC (10% ether–pentane), IR (CCl_4), and retention time on GLC (15% SE-30, 80 °C) for 12 were identical with those of an authentic sample

Methyl 3-Oxobicyclo[3.2.1]octane-6-*endo*-carboxylate (13). Keto acid 7 (0.51 g, 3.04 mmol) was covered with ether (15 mL, anhydrous), and the mixture was cooled as a freshly prepared ethereal solution of diazomethane was added. When a permanent yellow color was obtained, the ether was removed to yield a yellow oil which was purified by vacuum distillation (100 °C, 0.35 mm). A clear liquid (0.53 g, 97%) was obtained: IR (CCl_4) 1730 (ester C=O) and 1710 (ketone C=O) cm^{-1}; NMR (CCl_4) δ 3.68 (s, 3, $-OCH_3$) and 3.3–1.8 (broad m, 11); mass spectrum, parent *m/e* 182.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.90; H, 7.69. Found: C, 66.02; H, 7.55.

Methyl 2,2,4,4-Tetradeuterio-3-oxobicyclo[3.2.1]octane-6-*endo*-carboxylate (14). A sample of 13 (0.228 g, 1.25 mmol) was dissolved in deuteriomethanol (5 mL) containing a catalytic amount of sodium methoxide (~15 mg). After the solution was allowed to stand for 48 h at 20 °C, the solvent was removed in vacuo and the residue obtained was dissolved in ether. The ether solution was washed with deuterium oxide and dried, and the solvent was removed in vacuo to yield a clear liquid: IR (CCl_4) 1730 (ester C=O) and 1710 (ketone C=O) cm^{-1}; NMR (CCl_4) δ 3.68 (s, 3, $-OCH_3$) and 3.0–1.8 (broad m, 7); mass spectrum, parent *m/e* 186.

Chemical Degradation of Lactone 5. 2-Oxobicyclo[3.2.1]octane-7-*endo*-carboxylic Acid (15). Lactone 5 (0.40 g, 2.6 mmol) was oxidized with ruthenium tetroxide by the procedure used in the oxidation of 4. In this manner a semisolid was obtained which gave two spots on TLC (50% ether–pentane), one of which corresponded to the lactone. The material was chromatographed on silica gel (60 g, 50 × 5 cm), and 0.11 g (44%) of 15 was isolated from 20% ether–hexane fractions. The compound was crystallized from ether–hexane and sublimed (92 °C, 0.35 mm) to yield 15: mp 148–149.5 °C; IR ($CHCl_3$) 1710 (acid C=O and ketone C=O) and 3520 (acid OH) cm^{-1}.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.25; H, 7.20. Found: C, 64.12; H, 7.12.

A sample of 15 was treated with diazomethane, and the ester was obtained as a clear oil: IR (CCl_4) 1735 (ester C=O) and 1715 (ketone C=O) cm^{-1}.

Equilibration of Bicyclic Lactones in Acid Medium. Lactones 3–5 (3.0 mmol) were separately treated with concentrated sulfuric acid (10 mL) at 25 °C. At timed intervals aliquots (2.0 mL) were removed

Table IV

time, h	products detected by TLC % 3	% 4	% 5
Rearrangement of 3 in Concd H_2SO_4 at 25 °C			
2			
5			
12[a]	~10	85	<5
24	0	79	21
120	0	55	45
Rearrangement of 4 in Concd H_2SO_4 at 25 °C			
2			
5			
12[a]	0	>90	<10
24[a]	0	>75	<25
120	0	55	45
Rearrangement of 5 in Concd H_2SO_4 at 25 °C			
2	*b*	*b*	*b*

[a] Estimated by NMR line integration. [b] Yields not determined.

and diluted with water (40 mL). The solution was extracted with four portions of chloroform. The extracts were combined, washed with saturated sodium bicarbonate solution, and dried. The solvent was removed in vacuo to yield a crude solid (~80 mg). The products were identified by comparison on TLC (75% ether–hexane) with the previousiy isolated lactones. Product yields were obtained by chromatography on silica gel (10 g) in the manner described above, or in some cases they were estimated by relative peak areas of the C_2 proton in **5** and the C_3 proton in **4** in the NMR spectrum of the crude product (see Table IV).

Longer reaction times caused substantial decomposition, thus precluding an accurate determination of products at equilibration.

Acid-Catalyzed Cyclization of 1 with Deuteriosulfuric Acid. The methods used for the preparation and isolation of products in the isotopic study were identical with those used previously except that concentrated deuteriosulfuric acid (99.5%, Diaprep Corp.) was used as the strong acid. Compound **3**-d_1 was obtained: mp 205–206 °C; NMR ($CDCl_3$) δ 4.67 (broad t, 1, J = 2 Hz, half-height width = 8 Hz, $C_{6\text{-exo}}$-H), 2.50 (m, 2), and 2.0–1.2 (broad m, 8); mass spectrum, parent m/e 153, base m/e 80, m/e 135 (P − H_2O), 125 (P − CO), 109 (P − CO_2), 96, 67, and 66. Compound **4**-d_1 was obtained after sublimation (105 °C, 0.5 mm): mp 237–238 °C; NMR ($CDCl_3$) δ 4.60 (narrow m, 1, half-height width = 6.0 Hz, C_3-H) and 3.20–1.60 (broad m, 10); mass spectrum, parent m/e 153*, base m/e 66, m/e 135 (P − H_2O), 125 (P − CO), 109 (P − CO_2), 96, 81, 80, and 67.

Acid-Catalyzed Cyclization of 2-*exo*-Methylbicyclo[2.2.2]-oct-5-ene-2-*endo*-carboxylic Acid (16). The acid **16** (1.0 g, 6.0 mmol) was added to concentrated sulfuric acid (10 mL), and the solution was shaken vigorously for 10 min. A homogeneous yellow solution was obtained which was poured over ice (50 g). The resulting mixture was extracted four times with ether. The extracts were combined, washed with a saturated solution of sodium bicarbonate, and dried. The solvent was removed in vacuo, and 0.88 g (88%) of white solid resulted. The solid was chromatographed over silica gel (40 g), and a component was isolated from the 20% ether–petroleum ether fractions. This material (0.21 g, 12%) had spectral and physical properties identical with an authentic sample of 2-*exo*-methyl-6-*endo*-hydroxybicyclo[2.2.2]octane-2-*endo*-carboxylic acid γ-lactone (**17**).[33] A second component (0.72 g, 72%) was isolated and crystallized from acetone–hexane to yield lactone **18**: IR ($CHCl_3$) 1730 cm^{-1} (lactone C=O); NMR ($CDCl_3$) δ 4.6 (m, 1, $C_{3(e)}$-H), 1.20 (s, 3, CH_3), and 3.2–1.4 (broad m, 8 H).

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