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BASE HYDROLYSIS OF HALOLACTONES IN THE BICYCLO(2.2.1)HEPTYL AND BICYCLO(2.2.2)OCTYL SYSTEMS

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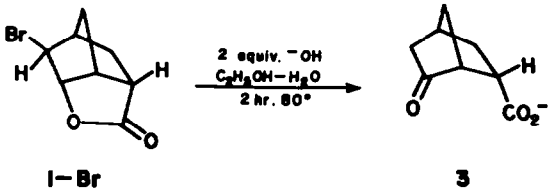
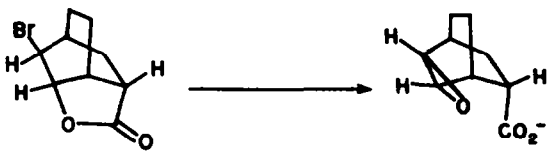
Abstract—The mechanism of ketocarboxylic acid formation in the base treatment of bicyclo[2.2.1]heptyl halolactones has been determined. On the basis of stoichiometry, kinetics, effect of leaving group, and isotopic labeling experiments, a dehydrohalogenation mechanism is proposed in which cleavage of the carbon–halogen bond precedes that of the carbon–hydrogen bond in the transition state. The relationship between E1-like and *syn*-E2 transition states in these systems is discussed.

In the bicyclo[2.2.2]octyl series base treatment of the halolactones yields oxidocarboxylic acids. The difference in behavior between the two systems is rationalized on the basis of molecular geometry.

During the course of our studies on solvolytic reactions of bridged bicyclic lactones[1] we observed a striking difference in behavior towards base between 5 - *exo* - bromo - 6 - *endo* - hydroxybicyclo[2.2.1]heptane -2 - *endo* - carboxylic acid γ-lactone (1-Br) and 5 - *exo* - bromo - 6 - *endo* - hydroxybicyclo[2.2.2]octane - 2 - *endo* - carboxylic acid γ-lactone (2-Br):



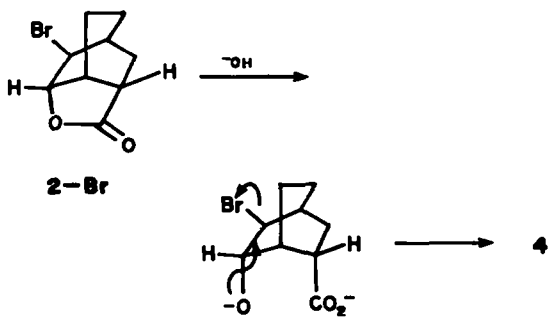
1-Br 3



2-Br 4

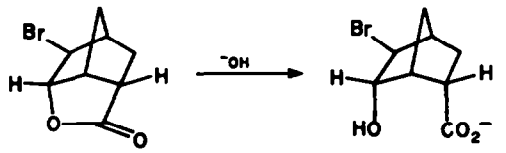
Analogous results were obtained with the iodolactones and tosyloxylactones 1-I, 1-OTs and 2-I and 2-OTs.

Reaction 2-Br→4 is not surprising and can be rationalized in terms of base hydrolysis of the γ-lactone and intramolecular displacement of bromide anion from the resulting *trans*-bromohydrin 5.



2-Br 5 4

Formation of 6 - ketobicyclo[2.2.1]heptane - 2 - *endo* - carboxylic acid (3) is unexpected, especially relative to the apparently feasible oxide formation from the presumed *trans*-bromohydrin 6.



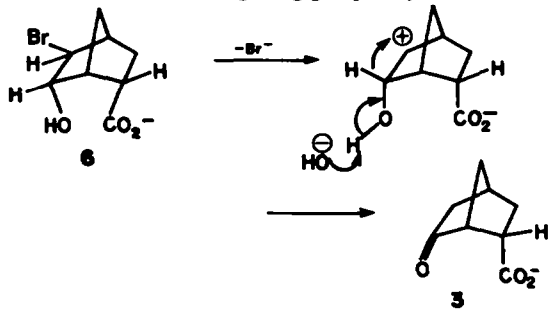
1-Br 6

This reaction has been observed by others but no rationalization has been adduced to explain the difference in behavior between the two systems.[2-5]

Ketone formation from *cis* halohydrins is well known. For example, Bartlett observed that *trans*-2-chlorocyclohexanol yielded cyclohexane-1,2-oxide upon base treatment while *cis*-2-chlorocyclohexanol yielded cyclohexanone.[6]

A priori, three possible pathways may be considered for 1-Br→3. First, 1-Br could yield 5,6-*endo*-oxobicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (7) which might rearrange under the reaction conditions to 3. Second, ionization of the C–Br bond might occur followed by hydride shift of the C_6-hydrogen. Third, base dehydrobromination and ketonization of the resulting enol could account for ketone formation. The first mechanism was immediately disposed of by independent synthesis of 7 according to the method of Christol *et al.*,[7] and demonstration that it was not converted to 3 under the reaction conditions.

The second mechanism is actually a pinacolic type reaction in which the migrating group is hydride ion.

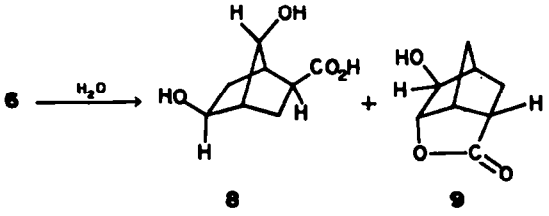


6 3

The *exo-cis* hydride shift is frequently proposed in the norbornane series and has been invoked to explain the formation of norbornanone from the 2,3-*cis*-*exo*-diol.[8] Certain such processes have been shown to involve extensive skeletal rearrangement.[9]

Two obvious characteristics of the pinacolic mechanism for 1-Br→3 are (a) it should not show a kinetic dependence upon base unless the alkoxide anion were more reactive than the free alcohol, and (b) a deuterium atom should be transposed from C_6 to C_5.

Postulate (a) was tested by first establishing the course of the reaction with respect to products in the case of the sodium salt of 1 in the absence of extraneous OH ion. Bromolactone (1-Br) was dissolved in ethanol and treated with one equivalent of 0.4 N NaOH. Solvent was removed at 50° *in vacuo* and the resulting sodium salt was dissolved in water and heated at 95° for 6 hr.



8 9

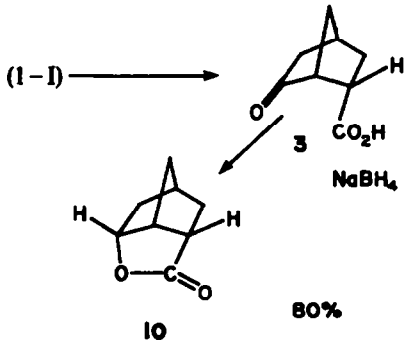
No formation of ketone 3 was observed under these conditions. The product mixture consisted of 15% of unreacted starting material, 10% of 5 - *exo* - 7 - *syn* - dihydroxybicyclo[2.2.1]heptane - 2 - *exo* - carboxylic acid (8),[10] and 8% of 5 - *exo* - 6 - *endo* - dihydroxybicyclo[2.2.1]heptane - 2 - *endo* - carboxylic acid γ-lactone (9).[11,12] Similar results were obtained using the iodolactone as its sodium salt. Products analogous to 8 and 9 have been obtained in the acetolysis of 1-OTs, and their formation may be understood in terms of addition to the derived carbonium ion.[13] Under aqueous condition the 3,7-γ-lactone undergoes hydrolytic cleavage. One may conclude that clean formation of 3 does not appear to agree with the intervention of the norbonyl carbonium ion in the decomposition of 6.

In order to gain information about the mechanism of reaction of 1 and 2 with base a detailed product and kinetic study was carried out. Since one equivalent of base is consumed in hydrolytic cleavage of the lactone ring, a second equivalent of base is necessarily responsible for the formation of 3.

Reaction of halolactones 1 *and* 2 *in two molar equivalents of base*

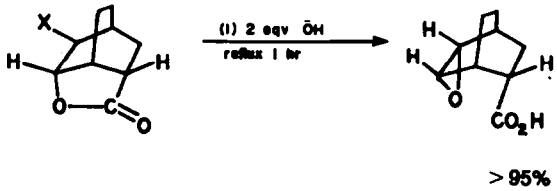
Reaction of 1-Br, 1-I or 1-OTs in two equivalents of base gave a mixture of two products. In a typical experiment, iodolactone (1-I) was heated on a steam bath for 1 hr in a 40% ethanol–water solution containing two molar equivalents of NaOH. After chromatography 6 - ketobicyclo[2.2.1]heptane - 2 - *endo* - carboxylic acid (3) 79% was separated. It was identified by its mp,[2] and indicative absorptions in the IR and NMR spectra. Ketoacid 3 was reduced with sodium borohydride to the known 6 - *endo* - hydroxybicyclo[2.2.1]heptane - 2 - *endo* - carboxylic acid γ-lactone (10).[2]

A second compound (≃3%) was identified as hydroxylactone 9, the compound which was isolated in higher yields upon hydrolysis of 1 in one molar equivalent of base.

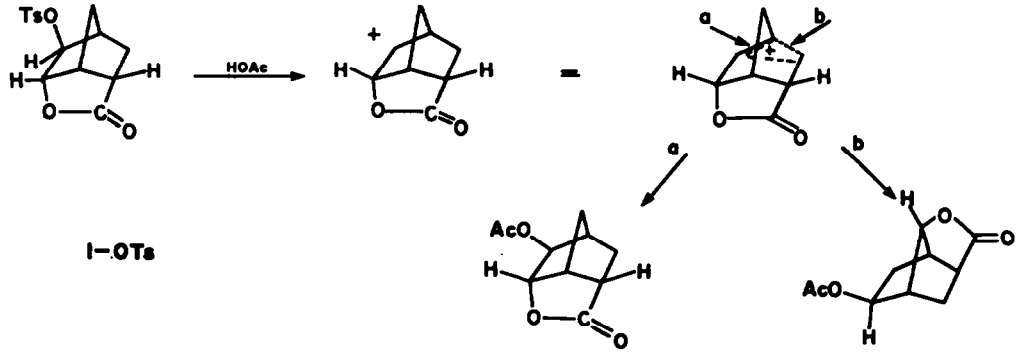


Under similar conditions, the bromolactone 1-Br yielded 83% of ketoacid 3 and ≃5% of 9 while the tosyloxylactone 1-OTs yielded about 70% of 3.

Hydrolysis of bicyclooctylhalolactone (2-Br, 2-I) under similar conditions (2 equiv of NaOH in EtOH–H_2O soln) gave no ketoacid, but quantitatively yielded an epoxy-



2 X=Br,I 4 >95%



1-OTs

acid, 5,6 - *endo* - oxobicyclo[2.2.2]octane - 2 - *endo* - carboxylic acid (4). The structure of 4 was established on the basis of the following spectral and chemical evidence. The IR spectrum of 4 contained characteristic carboxylic acid absorption at 3500 (–OH) and 1700 cm^{-1} (acid C=O) and characteristic epoxide absorption at 1257 (C<O>C) and 849 cm^{-1} (C–H) bend for *cis*-epoxide). The NMR spectrum showed a downfield singlet at δ 11.80 for the acid proton and two downfield doublets at δ 3.25 for the C_5-*exo* and C_6-*exo*-protons.

Chemical proof of the structure of 4 as outlined in Chart 1 was attained by preparation of an authentic sample by epoxidation of bicyclo[2.2.2]oct - 5 - ene - 2 - *endo* - carboxylic acid (11). When the unsaturated acid was treated with perbenzoic acid in chloroform a crude solid was isolated which showed three spots on tlc. Chromatography of the crude product gave 58% of 5 - *exo* - 6 - *endo* - dihydroxybicyclo[2.2.2]octane - 2 - *endo* - carboxylic acid γ-lactone (12). The m.p., IR spectrum, and tlc of 12 were identical to similar data recorded for an authentic sample.[11] It should be pointed out that Crundwell and Templeton[12] have reported that hydroxylactone 12 was the sole product obtained upon peracid treatment of the same starting material. However, in this case, chromatography of the crude product also yielded two other compounds, albeit, in small yield. One was *endo*-epoxyacid 4 (12%) which gave the same m.p. and IR spectrum as the product obtained by hydrolysis of halolactone 2. The other component isolated in low yield (3%) proved to be the *exo*-epoxyacid 13. This structure was verified by esterification with diazomethane to yield the methyl ester which had boiling point and spectral data identical to those recorded for an authentic sample[12] of methyl *exo* - 5,6 - oxo - bicyclo[2.2.2]octane - 2 - *endo* - carboxylate (14).

Other evidence for the structure of *endo*-epoxyacid 4 was adduced by interrelating the corresponding epoxyesters. The epoxyacid 4, the product of hydrolysis of halolactone 2, was esterified with diazomethane to yield methyl - *endo* - 5,6 - oxobicyclo[2.2.2]octane - 2 - *endo* - carboxylate (15). Physical and spectral data recorded for 15 were the same as those for the minor product (24%) isolated from the epoxidation of methyl bicyclo[2.2.2]oct - 5 - ene - 2 - *endo* - carboxylate (16). The major product (51%) in the epoxidation was assigned structure 14 (see Chart 1) on the basis of spectral data and composition.

Synthesis of deuterium labeled compounds

To determine the fate of the C_6-*exo* hydrogen during base hydrolysis of norbornyl halolactones 1-Br and 1-I, 5 - *exo* - bromo - 6 - *exo* - deuterio - 6 - *endo* - hydroxybicyclo[2.2.1]heptane - 2 - *endo* - carboxylic acid γ-lactone (d_1-1-Br) was prepared from ketoacid 3. The first reaction involved bromination of 3 with pyridinium hydrobromide perbromide[14] or bromine in acetic acid at 80–90°. This afforded a good yield (81%) of 5 - *exo* - bromo - 6 - ketobicyclo[2.2.1]heptane - 2 - *endo* - carboxylic acid (17).

The assignment of *exo* stereochemistry to the bromine was based on analogous brominations of norcamphor[15] and substituted norbornanones[16] which gave *exo*-bromination exclusively. In addition, the NMR spectrum which had a downfield singlet for the acid proton also showed a downfield doublet (3 Hz) at δ 4.1 for the

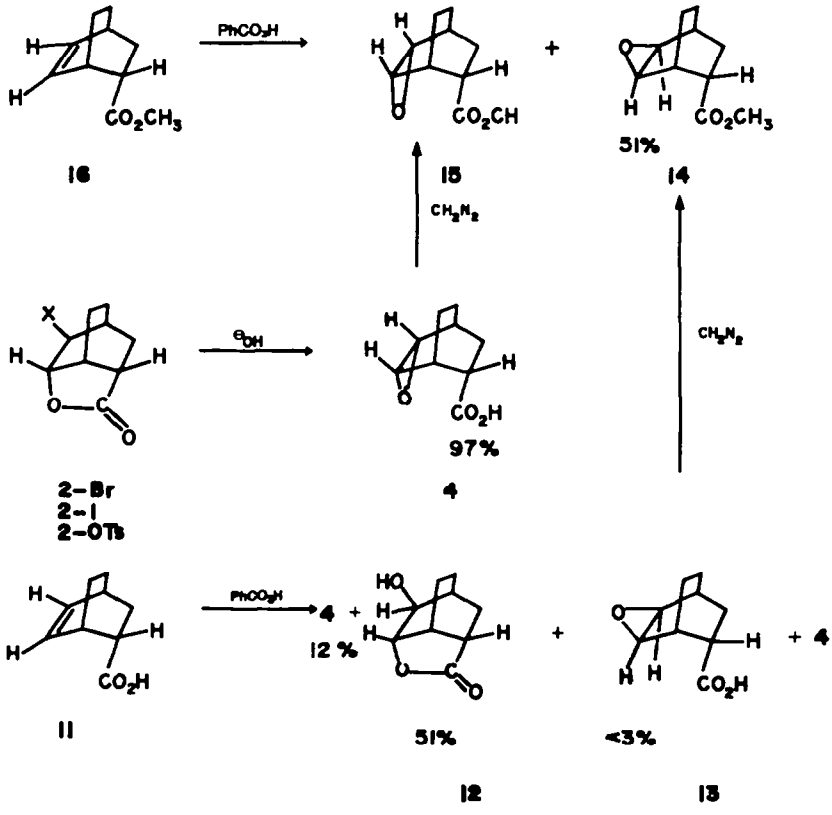
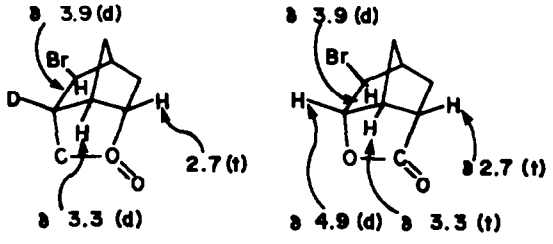


Chart 1. Correlation of structures of bicyclo[2.2.2]octyl epoxyacids.

C_5-*endo* proton. The doublet arises from long range coupling with the C_7-*anti* proton. This phenomenon has been well established by Meinwald[16] for similar α-bromonorbornanones which show long-range coupling constants from 3 to 4 Hz.

The bromoketoacid 17 was then reduced with sodium borodeuteride in isopropyl alcohol to yield 75% of deuteriobromolactone d_1-1-Br. In a similar manner, reaction with sodium borohydride yielded (70%) of the normal bromolactone 1-Br. The IR spectra of the deuterated compound d_1-1-Br and 1-Br contained characteristic absorptions at 1785 cm^{-1} (C=O) for the lactone and 665 cm^{-1} (C–Br) for the carbon–halogen bond. The IR spectrum of a concentrated solution of d_1-1-Br showed a C–D stretch at 2250 cm^{-1}. The NMR spectrum showed a downfield doublet ($J_{H_5\text{-}endo\text{-}H_7\text{-}anti}$ = 2 Hz) at δ 3.9 for the C_6 proton and a doublet ($J_{H_2\text{-}exo\text{-}H_1}$ = 4 Hz) at δ 3.3 for the C_1 proton. The assignment of protons to their respective absorptions was made on the basis of a previous study[17] on the complete NMR analysis of halolactones, 1-Br and 1-I. Moreover, by comparison of the NMR spectrum of d_1-1-Br with the spectrum of bromolactone 1-Br, the position and stereochemistry of the deuterium was definitely fixed at C_6-*exo*. The main difference between the NMR spectrum of d_1-1-Br and 1-Br was the presence of a downfield doublet ($J_{H_6\text{-}exo\text{-}H_1}$ = 5 Hz) at δ 4.9 for the C_6-*exo* proton in the spectrum of the latter. In relation to this the H_1 proton appeared as a triplet in the spectrum of d_1-1-Br. One other important feature in the spectrum of d_1-1-Br was the presence of a weak resonance at δ 4.9 for the C_6-*exo* proton due to a small percentage of the undeuterated halolactone. The amount of undeuterated contaminant was estimated as approximately 10% from relative peak areas in the NMR. This estimate was verified by deuterium analysis[18] of the deuteriolactone sample which was found to contain 9.97% D. Since analysis of a pure sample of d_1-1-Br should be 11.11% D, 10.0% of the sample was undeuterated.

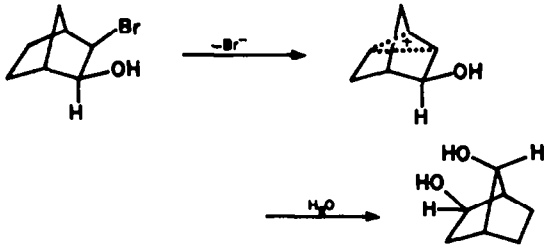


d_1–1–Br — 1–Br

In conjunction with this fact, the elemental analysis was in agreement with the structure d_1-1-Br, if consideration was made for the 10% impurity in the sample. Finally, the mass spectrum gave the correct parent ion at *m/e* 219 and 217.

Mechanism of ketoacid formation

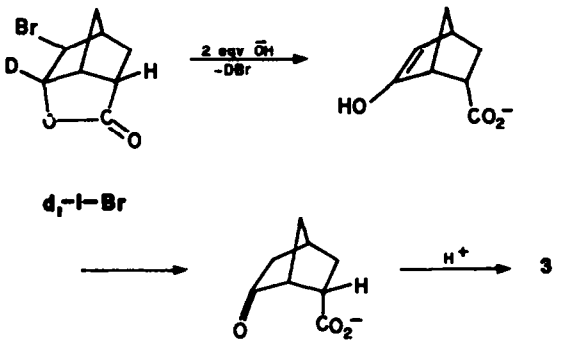
The effect of base concentration upon reaction products provided revealing information concerning the mechanism of ketone formation from halolactones 1-Br and 1-I. When the substrate to base ratio is 1:1, there is IR and chemical evidence that the reactant is actually the hydroxycarboxylate salt of 1 in a neutral solution. When this solution was heated, the products as mentioned above, although obtained in poor yield, were hydroxylactone 9, and in the case of the bromolactone, dihydroxycarboxylic acid 8. These compounds are normally expected from a solvolytic process and their formation can be explained by either a "nonclassical" norbornyl cation or a classical cation which undergoes nucleophilic attack at C_4 or C_5 leading to 8 and 9, respectively. Good analogy for formation of rearranged dihydroxyacid 8 in aqueous media has been reported by Krieger[20] who has observed that solvolysis of 2 - *exo* - bromo - 3 - *exo* - norbornanol in water yields 7 - *syn* - 2 - *exo* - dihydroxynorbornane. In this case a cationic intermediate similar to 18 can be evoked to explain the formation of rearranged *syn*-diol. The only difference between these two solvolysis reactions is that rearrangement occurs with the opposite stereochemistry, i.e. the *trans*-bromohydrin rearranges to an *anti*-diol 8. A reaction following the same stereochemical course has been reported by Roberts *et al.*[21] for the solvolysis of *trans*-2,3-dichloronorbornane. The absence of ketoacid 3 in neutral media indicates a hydride shift process is not competitive with cationic rearrangement 8 and direct solvent capture to give 9.



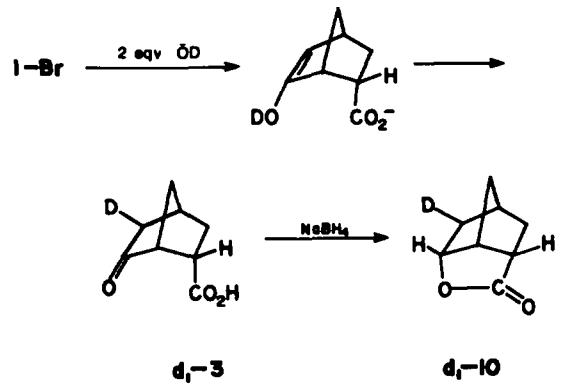
When a second equivalent of hydroxide was added to the solution the reaction course changed and a good yield (80%) of ketoacid 3 was obtained. Besides 3 a low yield (3%) of hydroxylactone 9 was isolated upon chromatography of the crude mixture. The decrease in 9 is not unexpected, since increases in base concentrations are usually associated with a decrease in products arising via an unimolecular (SN1)[22] process. However, what is surprising is that a change from a neutral to a ≃0.7 N NaOH solution produces such a marked formation of ketoacid 3.

To check quantitatively whether there was any direct relationship between the base concentration and the rate of ketone formation, the OH ion concentration was varied (0.05–0.10 M) and the time required for disappearance of 25% of the second equivalent of base was recorded. Since the moles of ketone formed and the moles of base lost were equal, monitoring the decrease in base concentration seemed an adequate method for following the reaction rate. For dual runs it was determined that the quarter time for reaction *doubled* for a *proportional* decrease in base concentration. In fact, reaction of both halo- and tosyloxy-lactones in base showed excellent second order kinetics up to 60% reaction.

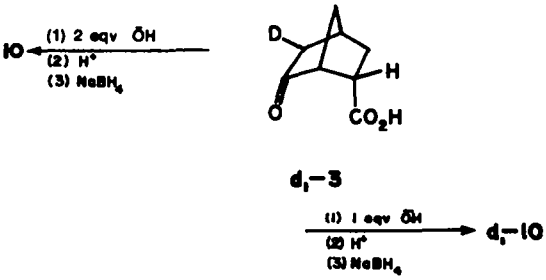
Assuming for the moment that formation of 3 results from an E_2 dehydrohalogenation the fate of deuterium during the reaction of 6-*exo*-deuteriolactone d_1-1-Br might potentially yield some relevant information. Not only should deuterium be lost if an elimination takes place, but the rate of ketone formation from 1-Br would be expected to be faster than the reaction of the deuterated analog d_1-1-Br. When d_1-1-Br was treated with base, ketoacid 3 was obtained which was reduced to the undeuterated lactone 10. Conversely, if the halolactone



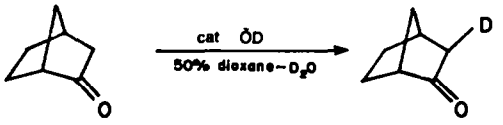
1-Br was reacted in a deuterated base-solvent system (OD–D_2O), a ketoacid d_1-3 resulted which upon reduction with sodium borohydride yielded 5-*exo*-deuterated lactone d_1-10 (100% d_1 as determined by D analysis). This latter result seems reasonable, since an elimination reaction would form an intermediate enol which would tautomerize to the ketone with α-deuteration occurring at the more accessible *exo*-face of the norbornyl skeleton.[23] Although these two results agree with an elimination mechanism, they are not unambiguous in light of experiments which indicate the 5-*exo*-proton of the product undergoes rapid exchange during reaction of 1-Br.



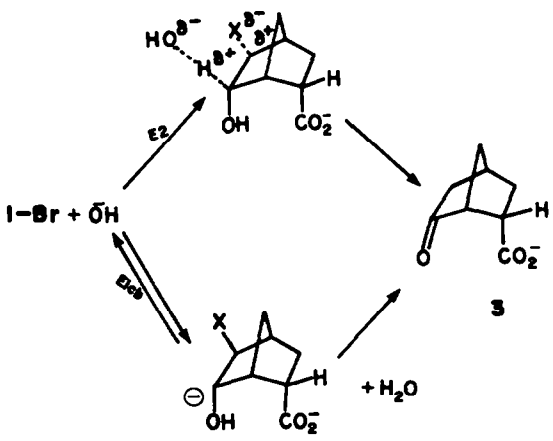
Specifically, when the deuterated ketoacid d_1-3 was treated with two equivalents of base under the same conditions used in the reaction of 1-Br complete loss of D resulted. In one equivalent of base where the keto-carboxylate salt is presumably present in neutral solution the D label was retained. The former experiment resembles the conditions present at the beginning of the reaction of 1-Br while the latter exchange experiment represents conditions at the conclusion of reaction. Therefore, d_1-3 loss of deuterium during hydrolysis of d_1-1-Br or incorporation of deuterium during reaction of 1-Br could occur by either an elimination reaction or by α-proton exchange in the product 3.



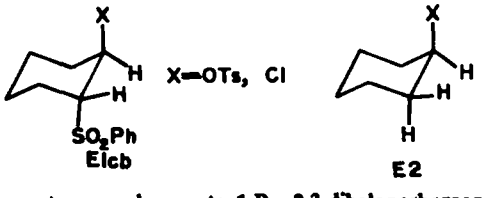
The validity of these exchange studies have been fortified by the work of other researchers who have observed rapid *exo*-deuterium exchange for substituted norbornanones[24] or norcamphor[25] in basic 50% dioxane–deuterium oxide solution. Even when catalytic amounts of deuteroxide are used at room temperature rapid exchange is observed.



Further experiments aimed at elucidating the elimination mechanism focused on differentiating between a concerted E2 of a two-step Elcb pathway. Since both mechanisms are consistent with observed second-order kinetics, other experimental approaches, such as the effect of leaving group and solvent on reaction rate and kinetic isotope effect were used as a basis for choice between these possibilities.

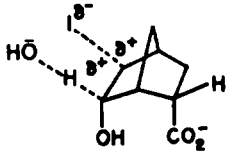


Evidence in favor of a one-step concerted mechanism for dehydrohalogenation is the observed dependence of leaving group on rate of ketone formation. If a two-step (Elcb) process were occurring, the rate determining step would be carbanion formation and the leaving group would be expected to have very little effect on the rate. This seems to be the case for the Elcb elimination of HX from *trans*-2-chlorocyclohexyl phenyl sulfone and *trans*-2-tosyloxycyclohexyl phenyl sulfony which show nearly identical *syn*-elimination rates.[26] On the other hand, cyclohexyl tosylate undergoes E2 elimination more rapidly than cyclohexyl chloride.[26] In the case of 1-Br, a change in leaving group to tosylate increases the rate by a factor of greater than 20.



In systems analogous to 1-Br, 2,3-dihalonorbornanes, LeBel has obtained good evidence for E2 reactions in that the rate of *syn*-dehydrohalogenation in sodium pentoxide shows a definite dependence on leaving group with HBr eliminated approximately 25 times faster then HCl. The fact that bromide is a better leaving group than

chloride is also consistent with a concerted E2 elimination. Surprisingly, the order of leaving groups in the reaction of 1 was OTs > Br > I. The unusual observation that iodine is a poorer leaving group than bromide can be understood if some degree of concertedness in the elimination is assumed. In the transition state for *syn*-elimination the leaving group and incoming base are *syn*-coplanar. With this geometry, steric repulsion between the larger iodine atom and base may be important and this factor could cause the observed order of reactivity, i.e. Br > I. An alternate explanation for the relative reactivity of the halolactones is based on dipolar effects. In a *syn*-E2 process iodine being more polarizable than bromide would develop greater separation of charge in the transition state. Since base and leaving group are on the same side of the molecule, dipolar repulsion between base and iodine may destabilize the transition state for elimination (19) in the case of the iodolactone. Support for the latter interpretation derives



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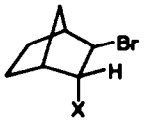
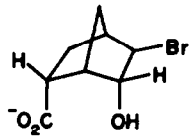
from solvent effects where a change of solvent from 40% ethanol–water to ethanol reverses the iodine–bromide order and iodolactone (1-I) reacts faster in ethanol. Presumably, the more polar solvent favors greater C–X bond polarization and larger dipolar repulsion would result in this aqueous solvent system. In ethanol, ionization of C–X is not as well developed in the transition state and normal leaving group trend is observed.

Additional evidence for a concerted mechanism relies on base strength and type of solvent used in reaction 1-Br. Elcb processes are favored in strong bases and in solvents which do not favor ionization.[22] As observed by LeBel,[27] even in the presence of a base as strong as sodium pentoxide, the dehydrohalogenation of 2,3-dihalonorbornanes most probably proceeds via an E2 mechanism. Since 1-Br and LeBel's compounds (see below) are structurally similar in that both have a β-hydrogen activated by an electronegative substituent and the same leaving group, it is unreasonable to entertain a carbanion intermediate in reaction of 1-Br with a base such as hydroxide ion in an ethanol–water solvent system.



X=Br,Cl

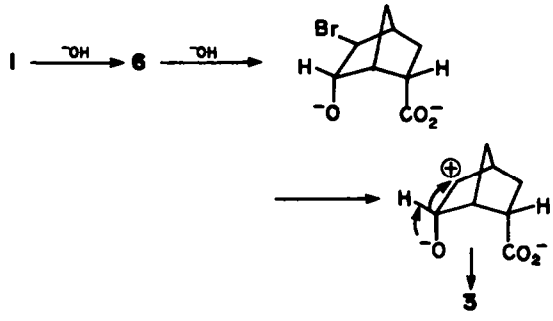


I(X=Br)

Although a bimolecular E2 reaction best fits the experimental results, a spectrum of bimolecular transition states can exist in which the relative degree of C–H and C–X bond breaking may differ. Three types of transition states (see below) can be visualized for an E2 process according to the bond changes, but all represent reactions which are still concerted in the sense that one bond fission cannot occur without the other.

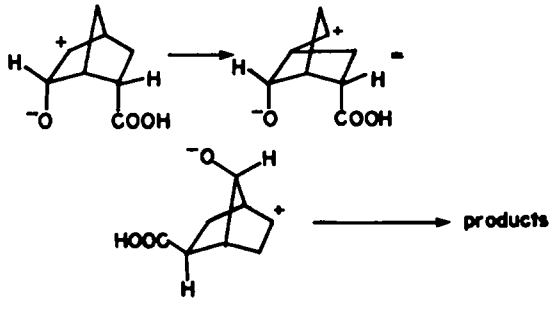
The β-deuterium isotope effect for 1-Br was $k_H/k_D = 1.67 \pm 0.05$ at 50°. Usually for a concerted E2 reaction where the C_β–H bond is substantially elongated in the transition state, isotope effects are much larger and normally vary from 4 to 8. For instance, DePuy *et al.*[28] have observed a $k_H/k_D = 5.6$ at 50° for the *syn*-E2 dehydrotosylation of 2-phenylcyclopentyl tosylate in KOtBu–HOtBu solution. LeBel[27] has found the value of $k_H/k_D = 3.6 \pm 0.1$ for the *syn*-dehydrohalogenation of 2,3-dihalonorbornanes, which he argues is in agreement with a concerted E2 reaction with the transition state lying slightly to the carbanion side (E1cb-like) of the "synchronous" state. By comparison, the isotope effect observed for 1-Br is small and is in better agreement with a transition state where there is little C–H bond polarization. In a similar ethanol–water solvent system, Shriner[30] has observed a $k_H/k_D = 1.3$ for the β deuterium isotope effect in the *E*1 elimination of HBr from 2-bromo-2,3-dimethylbutane. Therefore, a value of $k_H/k_D = 1.7$ would be expected for a E2 which possesses considerable carbonium ion character. It appears that the reaction of 1 is favored by factors (solvent and leaving group) which favor C–X cleavage and is relatively unaffected by factors which determine β proton abstraction (small β deuterium isotope effect). On this basis an E1-like transition state seems most appropriate for the dehydrohalogenation reaction.

A final mechanism which must be considered is a hydride shift mechanism occurring from the conjugate base of halohydrin 6.



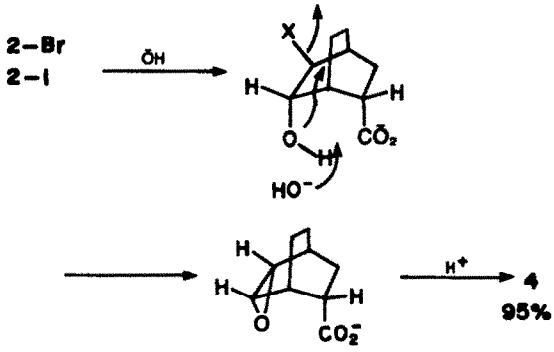
The second equivalent of base is required to generate the alkoxide ion. This process is in accord with the second order and the low isotope effect. A problem with this mechanism is the necessity of exclusive hydride shift as a mode of decomposition. In the closely related case of 6 rearrangement predominates. Analogous rearrangement in the case of the above carbonium would appear feasible.

One could perhaps argue that hydride shift would be greatly assisted by the resonance stabilization of the incipient carbonyl group as is true in normal pinacol rearrangements. This remains an unresolved point.



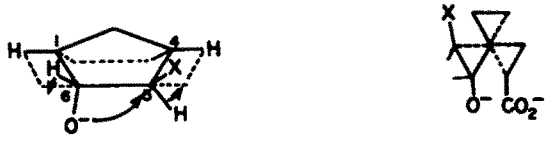
Mechanism of epoxyacid formation

In striking contrast to the behavior of 1-Br, is the reaction of the bicyclooctane halolactones 2-Br, 2-I which yield only *endo*-epoxyacid 4 upon treatment with base. Presumably the epoxyacid is formed via initial base hydrolysis of the lactone ring followed by *anti*-backside attack of oxide ion on the C–X bond. The formation of an epoxide is commonly observed from alkaline treatment of a cyclic *trans*-halohydrin.[6] As verification that 4 arose by an internal S_N2 transformation rather than by a solvolysis process followed by oxygen attack, the rate of epoxide formation was determined. Up to 75% reaction a linear second order plot was obtained with the iodolactone reacting almost twice as fast as the bromolactone. This order is a normal leaving group effect for an S_N2 process.



Factors affecting relative reactivity of 1-*X* vs 2-*X with base*

One explanation[1] offered for the difference in reactivity between 1 and 2 is based on torsional strain effects which have been used by Schleyer[29] to explain preferential *exo*-stereospecificity in the norbornane ring. Specifically, formation of the *endo*-epoxide in 1-Br would occur via a transition state in which the C_1,C_6 and C_5,C_4 C–H bonds are becoming eclipsed (**20**). This increase in torsional strain prohibits *endo*-epoxide formation and allows the elimination reaction to dominate. On the other hand, in the more flexible[30] bicyclo[2.2.2]octane system, torsional angles for relevant carbon–hydrogen bonds do not become as small as in the norbornane ring and intramolecular displacement by alkoxide is a favorable process.



20 Reacting Conformation of 2

EXPERIMENTAL

General. Uncorrected m.ps were recorded on a Thomas–Hoover capillary m.p. apparatus. IR spectra were taken on a Perkin–Elmer Model 337 Infracord and values are reported in reciprocal centimeters (cm^{-1}). Samples were run as dilute solns in NaCl cells (0.1 mm).

NMR spectra were recorded on a Varian A-60 spectrometer with TMS as an internal standard. Chemical shifts (δ) are reported in ppm downfield from TMS and coupling constants are given in hertz (Hz).

Mass spectra were recorded on a Varian CH-5 mass spectrometer and samples were examined at 70 eV ionization potential. Glc were recorded on an F & M Model 700 with columns (12 ft × 0.125 in.) containing Chromosorb was a support with a 30% silicon–rubber SE-20 coating. Tlc were prepared with Kiesel-Gel silica containing 5.0% $CaSO_4$. Iodine was used as a staining agent. Microanalysis was performed by Charles Beasley, Micro-Tech Laboratories, Inc., Skokie, Illinois 60076. All organic solns were dried with $MgSO_4$.

Reactions 5-substituted lactones in one equivalent of base

(1) Bromolactone (1-Br)[11] (0.85 g, 5.0 mmoles) was dissolved in EtOH (10 ml) and treated with 12.12 ml of 0.4015 N NaOH and the solvent was removed *in vacuo* below 50°; IR (Nujol) 3700–3300 (free and associated OH), 1540 cm^{-1}.

The resulting solid was dissolved in water (25 ml) and heated on a steam bath for 6 hr. The soln was cooled and acidified with HCl (5 ml of 1.0 N). The aqueous soln was extracted with three portions of EtOAc. The extracts were combined and dried and the solvent was removed *in vacuo* to yield 0.29 g of an oil. When the oil was washed with ether a solid precipitated. The soln was centrifuged and the solid collected (65 mg, 10%). The solid was suspended with anhyd ether and reacted with an ether soln of excess diazomethane. After the instantaneous reaction, ether was removed and the resulting oil showed one spot on tlc (50% ethyl acetate–hexane) which was coincident with the spot for an authentic sample[10] of the methyl ester of **8**. The oil was distilled (70°; 0.8 mm) to yield a solid dihydroxy ester of **8**: m.p. 119–121° [lit.[10] 122–123°]; IR ($CHCl_3$) 3610 (free OH), 3550–3200 (associated OH), and 1720 cm^{-1} (ester C=O).

The ether soln from which **8** was separated was evaporated and 0.24 g of a thick oil was obtained which gave three spots on tlc (40% ethyl acetate–hexane). The components were separated by preparative tlc. Bromolactone 1-Br (170 mg, 16%), **9** (51 mg, 8%) were the only products isolated and identified by comparison with authentic samples.

(2) Iodolactone (1-I)[11] (5.0 g, 18.9 mmol) was dissolved in EtOH (16 ml) and treated with 18.9 ml of 0.10 N NaOH. The soln was tested with phenolphthalein and found to be neutral. Water (5 ml) were added and the soln was refluxed for 18 hr. The soln was cooled, neutralized with HCl (20 ml of 0.1 N), and extracted with four portions of ether. The extracts were combined, washed with a $NaHSO_3$ aq, and dried. Upon concentration of the soln, a yellow oil was obtained which showed four components on tlc (10% ether–pentane). The oil was chromatographed on silica gel (110 g – 60 × 2.5 cm) and solid 1-I (1.67 g, 33%) was isolated from 10% ether–petroleum ether fractions while **9** was isolated from 50 to 100% ether–petroleum fractions. The material was crystallized from EtOAc–hexane to yield 0.373 g (19%) of **9**: IR ($CHCl_3$) 3600 (OH) and 1700 cm^{-1} (lactone C=O). The IR, tlc (20% ether–hexane) and m.p. of an authentic sample were identical to those of **9**. Two highly polar components (0.05 g) were isolated from 100% EtOAc fractions but could not be separated and were not investigated further. In another run, 1-I (2.64 g, 10.0 mmol) was dissolved in EtOH (15 ml) and 10.53 ml of 0.95 N NaOH (10 mmol) was added. The solvent was removed *in vacuo* at approximately 50° and the solid which formed was dissolved in water (50 ml) and heated on a steam bath for 6 hr. The soln was cooled, acidified with HCl (0.5 ml of 1 N) and extracted with seven portions of EtOH. The extracts were combined and dried and the solvent was removed *in vacuo*. The yellow oil obtained (0.58 g) gave four spots on the tlc (50% ether–hexane), one intense spot corresponding to iodolactone 1-I and one corresponding to **9**. Upon chromatography over silica gel (60 g) 0.31 g (20%) iodolactone 1-I was obtained from 20% ether–hexane fractions and 0.15 g (9%) of **9** was also isolated.

The aqueous soln was concentrated and the solid which remained was swirled in hot EtOAc. The heterogeneous mixture was filtered and the solvent was removed *in vacuo* to yield 50 mg of an oil which was not identified.

Reactions of 1-I *in two equivalents of base*

The iodolactone 1-I (15.0 g, 56.8 mmol) was dissolved in EtOH (40 ml) and added to an aqueous soln (100 ml) of NaOH (4.55 g, 114 mmol) and this soln was heated for 1 hr on a steam bath. The soln was cooled and 1 N HCl (60 ml) was added and the resulting mixture was extracted with four portions of EtOAc. The extracts were combined and dried and the solvent was removed *in vacuo* to yield a yellow oil which showed six spots on tlc (30% chloroform–petroleum ether). Upon standing, crystals formed in the crude product and were removed by filtration. The solid was crystallized from acetone–pentane to yield 3.8 g of 3: m.p. 101–103°; IR ($CHCl_3$) 3600–2400 (acid OH), 1745 (ketone C=O), and 1705 cm^{-1} (acid C=O); NMR ($CDCl_3$) δ 8.70 (broad s, 1, COOH) and 3.30–1.50 (broad m, 9).

The mother liquid was chromatographed over silica gel (110 g) and the following products were isolated.

Table 1.

Fraction (100 ml)	Elution solvent	Product (g)
12–22	50% ether–petroleum ether	2.7 m.p. 101–102°
27–34	100% ether	0.25
35–45	50% ethyl acetate–ether	0.40 mixture of two products

The major component had an IR spectrum identical to that of 3 obtained as crystals from the original soln. The two crops of ketoacid were combined and crystallized from acetone–hexane to yield 6.56 g (79%) of solid 3: m.p. 102–103° [lit.[2] 103–104°].

The second component (0.25 g, ≤3%) isolated had the same IR and m.p. as 9.

A mixture of two products (0.4 g, 5%) was isolated from more polar solvent fractions, but were not identified because they could not be separated.

Reaction of 1-Br under the same conditions yielded 83% of ketoacid 3 after chromatography. A small amount of 9 (< 5%) was also detected by IR spectrum of polar chromatography fractions. No attempt was made to purify this material.

Reactions of 2-I *in two equivalents of base*

Iodolactone 2-I[13] (2.5 g, 9.0 mmol) or the corresponding 2-Br (2.08 g, 9 mmol) was dissolved in EtOH and a NaOH (9.25 ml of 1.97 N, 18.0 mmol) and water were added to give a 70% EtOH–water soln. The soln was heated on a steam bath for 2 hr, cooled to rt, and tested with phenolphthalein indicator. The mixture was neutral indicating the consumption of 2.0 equivts of NaOH during reaction. After neutralization with dilute HCl (18.0 mmol) the soln was diluted with water (100 ml) and extracted with four portions of EtOAc. The extracts were combined and dried and the solvent was removed *in vacuo* to yield a solid (1.51 g, 100%). The material was repeatedly crystallized from an acetone–pentane soln to yield 1.42 g (96%) of 4: m.p. 148–149°; IR ($CHCl_3$) 3500 (acid OH), 1700 (acid C=O), 1257 (epoxide), and 849 cm^{-1} (*cis*-epoxide); NMR ($CDCl_3$) δ 11.80 (s, 1, COOH), 3.25 (q, 2 ), 2.72 (m, 1, C_2-*exo* H), and 2.4 to 1.4 (broad, m, 8). (Found: C, 64.41, H, 7.17. Calc. for $C_9H_{12}O_3$: C, 64.31, H, 7.15%).

Preparation of an authentic sample of endo-*epoxyacid* 4

Compound 11 (2.0 g, 13.1 mmol) in $CHCl_3$ (50 ml) was treated with 52.5 ml of 0.252 M perbenzoic acid in $CHCl_3$. The soln was kept 4 days at rt in the dark. After this time the starch–KI test was negative and the soln was washed twice with 10% KI aq, once with dil. $NaHSO_3$ aq. and dried. The soln was concentrated *in vacuo* and a solid was obtained which showed three spots on tlc (50% ether–pentane). The material was chromatographed over silica gel (130 g – 87 × 2.5 cm).

The material of m.p. 147–148° (12%) had an IR spectrum identical to that of 4, the product formed from alkaline reaction of 2. A mixture m.p. of both materials showed no depression.

The major component (1.28 g, 58%) was crystallized from acetone–hexane to yield white needles of 12: m.p. 231–236° [lit.[12] 231–235°].

The IR and tlc (50% ether–pentane) properties of 12 were identical to those previously reported.[12] Also, a m.p. of a mixture of the above material and an authentic sample of 12 showed no depression.

The third component, (13: ≈3%) was purified by sublimation, (105°, 0.8 mm); IR ($CHCl_3$) 1700 (acid C=O), 1250 (epoxide ), and 848 cm^{-1} (*cis*-epoxide).

For identification, this material was dissolved in ether and reacted with an excess of freshly prepared diazomethane. The ether was evaporated after reaction and 80 mg of an oil was obtained. The IR and tlc (5% ether–hexane) of the oil were identical to those of an authentic sample of 14.

Synthesis of endo-*epoxy ester* (15)

An ether soln of 4 (2.0 g, 11.9 mmol) was cooled to 0° and treated with freshly prepared diazomethane in ether. After instantaneous reaction, the ether was removed and the resulting yellow oil was vacuum distilled to yield 15 a clear liquid; b.p. 108–109° (1.1 mm); IR ($CHCl_3$) 1725 (ester C=O), 1257 (epoxide); and 847 cm^{-1} (*cis*-epoxide); NMR ($CDCl_3$) 3.64 (s, 3,), 3.12 (q, 2, ), 2.64 (m, 1, C_2-*exo*-H), and 2.5 to 1.4 (broad m, 8). (Found: C, 66.13; H, 7.86. Calc. for $C_{16}H_{14}O_2$: C, 65.96; H, 7.70%).

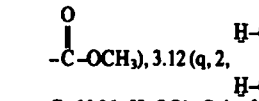
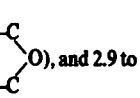
The tlc (5% ether–hexane), IR, and NMR of this product were identical to those recorded for the minor product isolated from epoxidation of unsaturated ester 16.

Epoxidation of unsaturated methyl ester 16

Compound 11[11] (2.0 g, 13.1 mmol) was dissolved in ether (20 ml) and treated with diazomethane soln. The solvent was evaporated at room temp. and the liquid remaining was vacuum distilled to yield 16 as a clear oil, b.p. 70–71° (1.3 mm); IR ($CHCl_3$) 1720 (ester C=O) and 700 cm^{-1} (); IR ($CDCl_3$) δ 6.13 (m, 2, ), 3.55 (s, 3, ), 3.0 to 2.4 (broad m, 3), and 1.86 to 1.10 (broad m, 6).

Table 2. Chromatographic separation of products from epoxidation of unsaturated *endo*-acid

Fraction (100 ml)	Elution solvent	Product (mg)
9–12	50% ether–petroleum ether	257, m.p. 147–148°
12–17	50% ether–petroleum ether	1282, m.p. 231–237°
19–22	100% ether	75 —

The ester **16** (3.88 g, 23.4 mmol) in $CHCl_3$ (100 ml) was cooled in ice and treated with 100 ml of 0.252 M perbenzoic acid soln in $CHCl_3$ over 0.5 hr. The mixture was washed with KIaq, twice with dil. $NaHSO_3$aq, and dried. The soln was concentrated to yield 4.1 g of a yellow oil which showed three spots on tlc (5% ether–pentane). The crude material was chromatographed on silica gel (100 g – 85 × 2.5 cm) with 20% ether–petroleum ether used as the eluant. Fractions 1–8 gave a yellow oil which showed one spot on tlc (5% ether–hexane). The oil was vacuum distilled to yield **14** 2.37 g (51%) as a clear liquid, b.p. 80–82° (0.45 mm) [lit.[14] 140–141° (19 mm)]; IR ($CHCl_3$) 1725 (ester C=O), 1150 (epoxide), and 851 cm^{-1} (*cis*-epoxide); NMR ($CDCl_3$) δ 3.67 (s, 3, ), 3.12 (q, 2, ), and 2.9 to 1.1 (broad m, 9). (Found: C, 66.06; H, 7.71. Calc. for $C_{10}H_{14}O_3$: C, 65.96; H, 7.70%).

A second yellow oil was obtained from fractions 10–16 which showed one spot on tlc (5% ether–hexane). The material was collected and vacuum distilled to yield 1.08 g (24%) of *endo*-epoxy ester **15**: b.p. 85–86° (0.4 mm). The IR, NMR, tlc, and elemental analysis of this material were identical to those recorded for the epoxy ester derived from halolactone **2**.

5-exo-Bromo-6-ketobicyclo[2.2.1]*heptane*-2-endo-*carboxylic acid* (**17**)

Ketoacid **3** (3.0 g, 19.44 mmol) was dissolved in glacial AcOH (20 ml) and heated to 70°. The soln was stirred while Br_2 (1.01 ml, 20.0 mmol) or pyridinium hydrobromide perbromide[14] (6.24 g, 19.5 mmol) was added. The temp. was increased to 90° and a gas (HBr) was evolved over 0.5 hr. The soln was heated and stirred for an additional 0.5 hr and then the AcOH was removed *in vacuo*. A brown solid was obtained which was partially dissolved in EtOAc (50 ml). The insoluble residue was dissolved in water (100 ml) and the aqueous soln was extracted with three portions of EtOAc. All EtOAc extracts were combined, washed with dil. $NaHSO_3$ aq and dried. The solvent was removed *in vacuo* and 4.0 g (88%) of a yellowish solid was obtained. The crude product showed only one spot on tlc (40% acetone–hexane) and was purified by crystallization from $CHCl_3$ to yield 3.60 g (81%) of **17**: m.p. 142–144°; IR ($CHCl_3$) 3500 (acid O–H), 1760 (ketone C=O), 1710 (acid C=O), and 670 cm^{-1} (C–Br); NMR (D_3CCOCD_3) δ 6.45 (broad m, 1, COO$\underline{H}$), 4.13 (d, 2, $I_{H_3\text{-}endo\text{-}H_7\text{-}anti}$ = 3H, $C_{5\text{-}endo}\underline{H}$), and 3.25 to 1.80 (broad m, 7). (Found: C, 40.82; H, 3.88. Calc. for $C_8H_9BrO_3$: C, 41.20; H, 3.90%).

5 - exo - *Bromo* - 6 - exo - *deuterio* - 6 - endo - *hydroxybicyclo*[2.2.1]*heptane* - 2 - endo - *carboxylic acid* - γ - *lactone* (d_1-1-Br)

Sodium borodeuteride (147 g, 35.0 mmol) was dissolved in 2-propanol (200 ml) which had been dried by distillation over Mg turnings. The soln was stirred and maintained at 50° to complete dissolution of the borodeuteride. When a homogeneous soln was obtained **17** (3.5 g, 15.0 mmol) was added in small portions over 5 min. The soln was stirred for 1 hr at 50° and overnight at room temp. The soln was cooled in ice and slowly acidified to pH = 3 with 10% HCl aq. Water (100 ml) was added and ≈ 250 ml of solvent was removed *in vacuo*. The remaining heterogeneous mixture (≈ 50 ml) was extracted with three portions of ether. The extracts were combined, washed with $NaHCO_3$ aq and dried. The soln was concentrated and 3.26 g of a yellow oil was obtained. The oil was crystallized from acetone–hexane to give 2.65 g (74.4%) of deuterated bromolactone **1**-d_1: m.p. 64.5–66.5°; IR ($CHCl_3$) 2250 (C–D), 1785 (lactone C=O), and 665 cm^{-1} (C–Br); NMR ($CDCl_3$) δ 3.88 (d, 1, $J_{H_5\text{-}endo\text{-}H_7\text{-}anti}$ = 2 Hz, $C_{5\text{-}endo}\underline{H}$), 3.26 (broad d, 1, $J_{H_2\text{-}exo}H_1$ = 4 Hz, C_1-$\underline{H}$), 2.67 (t, 1, $C_{2\text{-}exo}$-H), and 2.6 to 1.5 (broad m, 5); *mass spectrum* parent *m/e* 217, 219, base *m/e* 94, and major fragmentation peaks at 189, 191 (P–CO), 175, 173 (P–CO_2), 139 (P–Br), and 110. (Ionization potentials of 21, 14 and 8.5 eV were used in obtaining spectra.) (Found: C, 44.27; H, 4.23. Calc. for $C_8H_8DBrO_2$: C, 44.04; H, 4.58%, Deuterium Anal. Calc. for $C_8H_9DBrO_2$: D, 11.11. Found: D, 9.97%); 10.0% of undeuterated material present.

An identical procedure was used to prepare the undeuterated bromolactone. In this case **17** (3.5 g, 15.0 mmol) was reduced with $NaBH_4$ (1.33 g, 35.0 mmol) and 2.50 g (70%) of **1** was obtained: m.p. 64–65°; IR ($CHCl_3$) 1785 (lactone C=O) and 665 cm^{-1} (C–Br); NMR ($CDCl_3$) δ 4.90 (d, 1, $J_{H_6\text{-}exo\text{-}H}$ = 5.0 Hz, $C_{6\text{-}exo}$-H), 3.90 (d, 1, $J_{H_5\text{-}endo}$-$H_{7\text{-}anti}$ = 2.5 Hz, $C_{5\text{-}endo}$-H), 3.26 (t, 1, C_1-$\underline{H}$), 2.67 (broad m, 1, $C_{2\text{-}exo}$-$\underline{H}$), and 2.55 to 1.6 (broad m, 5).

Reaction of deuteriobromolactone d_1-1-Br *in two equivalents of base*

The bromolactone d_1-1-Br (0.75 g, 3.3 mmol) was dissolved in EtOH (5 ml) and added to a soln of NaOH (6.7 mmol) in water (7 ml). The mixture was heated on a stream bath for 1 hr and then cooled to 25°. The soln was acidified with 1 N HCl and extracted with three portions of $CHCl_3$. The extracts were combined, dried and the solvent was removed to yield 0.59 g of a yellowish oil. This material was chromatographed over silica gel (10 g) and 0.31 g (59%) of a solid was isolated from the 20% ether–petroleum ether fractions. The solid was crystallized in benzene–hexane to yield ketoacid **3**: m.p. 99–192°. Compound **3** (0.15 g, 1.0 mmol) was reduced with $NaBH_4$ to yield 0.145 g (93%) of **10** after sublimation (100°, 1.4 mm): m.p. 154–156° [lit.[2] 157–158°]; IR ($CHCl_3$) 1756 cm^{-1} (lactone C=O); NMR ($CDCl_3$) δ 4.94 (t, 1, $C_{6\text{-}exo}$-$\underline{H}$), 3.33 (t, 1, C_1–$\underline{H}$) and 2.8 to 1.3 (broad m, 8).

Reaction of iodolactone (1-I) *or bromolactone* (1-Br) *in deuterated solvent*

Iodolactone (1-I) (2.5 g, 9.45 mmol) or an equiv amount of bromolactone was powdered and added to D_2O containing two equivs of NaOEt (1.28 g, 18.9 mmol). The soln was heated on a steam bath for 1 hr and then cooled. The soln was neutralized with HCl (9.45 meq). The usual workup yielded 1.36 g of a yellow oil. After crystallization from benzene–petroleum ether soln 1.08 g (72%) of 5 - *exo* - deuterio - 6 - ketobicyclo[2.2.1]heptane - 2 - *endo* - carboxylic acid (d_1-3) was obtained: m.p. 104–106°; IR ($CHCl_3$) 3500–2500 (acid O–H), 1750 (ketone C=O), 1710 cm^{-1} (acid C=O); NMR ($CDCl_3$) δ 8.97 (broad m, 1, COOH), 3.30 to 2.50 (broad m, 3) 2.50 to 1.5 (broad m, 5). Deuterium Anal. Calc. for $C_8H_8DO_2$: D, 10.0. Found: D, 15.45. The deuterated acid d_1-3 (0.77 g, 5.0 mmol) was added slowly to isopropyl alcohol (90 ml) containing $NaBH_4$ (0.57 g, 15.0 mmol). The soln was stirred at 50° for 3 hr and then was acidified with HCl. The soln stood overnight and then sat. $NaHCO_3$ aq was added. The volume of soln was reduced to 10 ml *in vacuo*, then extracted with four portions of $CHCl_3$. The extracts were combined and dried and the solvent was removed. In this manner 0.68 g of a waxy solid was obtained. The material was sublimed (80°, 0.5 mm) and crystallized from acetone–hexane to yield **10**-d_1: m.p. 153–153.5° [lit.[19] 154–156°]; IR ($CHCl_3$) 2225 (C–D) and 1765 cm^{-1} (lactone C=O); NMR ($CDCl_3$) δ 4.79 (d, 1, $J_{H_5\text{-}exo\text{-}H}$ = 5 Hz, $C_{6\text{-}exo}\underline{H}$), 3.21 (broad t, 1, C–H), 2.75 to 1.20 (broad m, 7). Deuterium Anal. Calc. for $C_8H_9DO_2$: D, 10.00. Found: D, 10.01. Deuterated ketoacid **3**-d_1 (0.077 g, 0.5 mmol) was dissolved in EtOH (1 ml) and an equiv amount of NaOH (0.50 ml of 0.989 N). The soln was heated on a steam bath for 1 hr and allowed to stand overnight at room temp. The soln was neutralized with dil. HCl (0.5 ml of 0.99 N). The soln was diluted with water (40 ml) and extracted with four portions of EtOH. The extracts were combined and dried and the solvent was removed to yield 0.077 g of a solid. The solid was treated with $NaBH_4$ in isopropyl alcohol. The solid obtained after reduction gave an NMR spectrum identical to one recorded for **10**-d_1.

When **3**-d_1 was treated with two equivs of NaOH under identical conditions, a product was obtained which after similar reduction with $NaBH_4$ gave an NMR spectrum identical to one recorded for undeuterated lactone **10**.

Kinetic measurements. The rates of ketone formation **3** and intramolecular oxide fremation **4** were measured by following the rate of decrease in the concentration of the second equiv of OH ion. Second order rate constants were obtained from the slope of a plot of 1/(a-x) vs time

$$a = [\text{hydroxide}]_{\text{initial}} = [\text{substrate}]_{\text{initial}}$$

$$x = [\text{hydroxide}]_t$$

Table 3. Rate of loss of hydroxide ion during reaction of 1 and 2 at 50.0° ± 0.1°*

		40% ETOH-H_2O		EtOH	
Substrate	Conc	kx10¹(l-mol/min)**	k_{rel}	kx10¹(l-mol/min)**	k_{rel}
1-Br	0.10	2.62	1.00	0.098	1.00
	0.05	2.55			
1-I	0.10	1.60	0.62	0.25	2.54
	0.05	1.54			
d_1-1-Br	0.10	1.55	0.60	0.64	0.62
1-OTs	0.10	>33	>12.70	***	
2-Br	0.10	0.46	0.18		
2-I	0.10	0.88	0.34		

Time Required for Loss of 25% of Second Equivalent of Base at 50.0 ± 0.2°

[substrate]	[hydroxide]	$t_{1/4}$-min
1-I = 0.05	0.05	44
	0.10	21.5

*Although not graphed, rate constants were determined at 40.0 ± 0.2°C. The values were 0.086 and 0.056 l-mol/min for 1-Br and d_1-1-Br, respectively.

**Since maximum precision error reached 50 ppt, the error in reported rate constants is ± 5%.

***When base was added to 1-OTs in ethanol a precipitate formed which was assumed to be the insoluble carboxylate salt. This solid was water soluble.

when initial substrate concentration equaled initial base concentration. Fur runs carried out with unequal concentrations, the quarter time for base consumption is the only data reported. All measurements were repeated and precision for duplicate runs ranged from 5 to 50 parts per thousand.

A typical kinetic run was carried out as follows: A freshly recrystallized sample of halo- or tosyloxy-lactone 1 (1.00 mmol) was weighed in a volumetric flask (10 ml) and abs EtOH (4.0 ml) was added. At room temp. a standard soln of NaOH (2.00 mmol) was added to the ethanolic soln. The base was dispensed from a microburette with 0.01 ml gradations. The volume was raised to 10 ml by addition of water. The flask was quickly shaken, a 2 ml aliquot was removed, and the reaction was quenched by additional of 1.00 mmol of HCl. The volumetric flask was then stoppered and immersed in a constant temp. batch at 50.0 ± 0.1°. The time span between base addition and immersion of the flask in the bath was kept at 2 min. The aliquot removed before bath immersion was neutralized to a phenolphthalein endpoint with 0.0247 N HCl. In all cases, titration of the first aliquot indicated one molar equivalent (± 3%) of OH ion (1.00 mmol) was consumed initially. Aliquots (2 ml) were removed from the volumetric flask at intervals, diluted with cold water, and the excess base was neutralized with standardized HCl.

For the bicyclooctane derivatives, the last aliquot was removed after at least 75% of the second equiv of base had been consumed by reaction. No deviation from a second order straight line plot was observed up to that point. For the norbornyl halolactones deviation from a second order straight line plot occurred after 50–60% of the second equiv of base had been consumed. Consequently, the last aliquots were removed before 60% reaction. For the reactions in EtOH, the rate is followed only through the first 25% of reaction.

For reactions run in abs EtOH, the solvent was distilled from a NaOEt–EtOH sol and the NaOH pellets used were obtained from a newly opened container. Otherwise, the procedure was identical to the one cited above.

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