Structures of the γ-Lactones from the Acid-Catalyzed Cyclization of *exo*- and *endo*-2-Methylnorbornene-2-carboxylic acid

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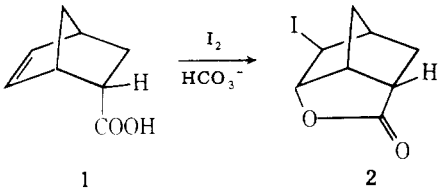
The structures of the two isomeric γ-lactones resulting from acid-catalyzed dehydration of 2-*exo*- and 2-*endo*-methylnorbornene-2-carboxylic acids have been proven by chemical degradation to 2,2-dimethylnorbornane and 7,7-dimethylnorbornane. The mechanism of formation of the lactones is discussed, and the implications of these results for related systems are presented.

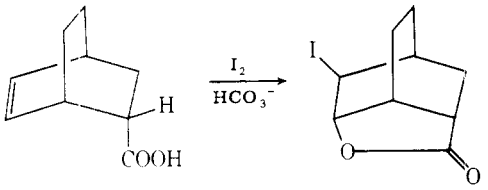
The relatively rigid geometry of the bridged bicyclic norbornyl system and the fixed positions in space of neighboring transannular atoms have caused these compounds to be used for estimation of proximity effects. Since these conformational features are important in enzymatic catalysis, bridged bicyclic compounds have been used as models for various enzyme systems. Recent examples of this strategy have been published by Loudon and Ryono[1,2] and also by Koshland et al.[3] One drawback in the use of these compounds as models is the pronounced tendency of the bicyclo[2.2.1]heptyl system to undergo cationic rearrangement. To a lesser extent this is also true of the bicyclo[2.2.2]octyl system. While this aspect of their behavior has led to many fundamental insights into the nature of cationic processes in general, in cases where the occurrence of such changes went unrecognized some serious misassignments of structure have resulted. Recently we reported, in a preliminary way, some examples of such errors in the bicyclo[2.2.1]heptyl[4] and bicyclo[2.2.2]octyl systems.[5] We report now the complete details of the establishment of these structures of rearrangement products in the first system. An accompanying paper deals with the second system. It is interesting to note that these isomers could not be satisfactorily distinguished by means of predominately modern physical methods, and ultimately we had to resort to chemical logic and chemical methods of a more or less classical type.

The particular rearrangement, which is the concern of this paper, is that occurring in cation-induced intramolecular lactone formation. A typical example of intramolecular lactone formation is halolactonization,[6] which has been widely used as an adjunct to the Diels–Alder reaction of dienophilic carboxylic acids[7] for the separation of exo and endo adducts. The method is based upon the valid assumption that only the endo orientation of the carboxyl group in **1** and **3** is correctly articulated in space for intramolecular cyclization with the olefinic double bond to yield a γ-lactone.

A priori, **1** and **3** could yield the six-membered 2,5-lactones, and in fact occasionally claims that they do have been made.



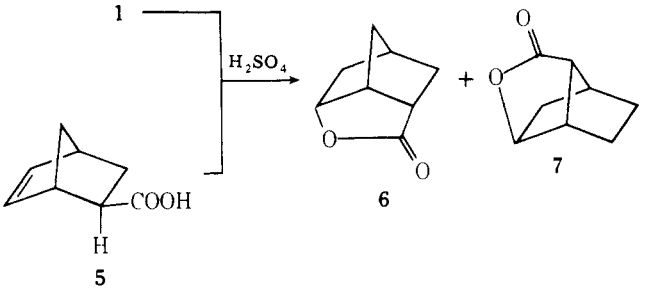
1 **2**



3 **4**

While the structure of **2** was rigorously established,[8] Risinger et al.[9] recently challenged this assignment. Subsequently, their erroneous interpretation of NMR data was pointed out by Oxner and Wege.[10] The δ-lactone corresponding to **4** has been claimed by Boehme et al.,[11] but attempts to repeat this synthesis by us and others have been unsuccessful.[12]

One could be misled into assuming that other electrophilic reagents might behave analogously toward **1** and **3** as do iodine or bromine; that is, the endo form yields a γ-lactone while no participation of the carboxyl group occurs in the exo case. However, this is not the case for exo and endo adducts **1** and **5** with a number of electrophilic reagents. Beckmann and Geiger[13] showed that both isomers yield the same equilibrium

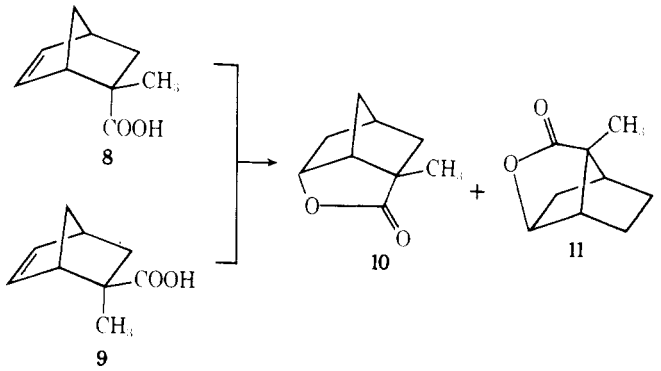


5 **6** **7**

mixture of γ-lactones **6** and **7** under conditions of acid hydration.

It has been shown also that **5** yields an acetoxy lactone upon reaction with lead tetraacetate[14] as well as with thallium triacetate.[15] In order for *exo*-norbornenecarboxylic acid **5** to form a lactone, a rearrangement of the initially formed carbocation must occur. It is exactly this proclivity of the norbornyl cation to rearrangement which has caused errors regarding the structure of lactones formed in this series.

The structures of the lactones from acid-catalyzed cyclization of *exo*- and *endo*-2-methylnorbornene-2-carboxylic acids **8** and **9**, respectively,[13] have been confused.[16] Unfortu-



8 **10** **11**

9

nately, these lactones of erroneous structure have been used recently as model compounds in the development of the concept of orbital steering by Koshland et al.[3]

Although Beckmann[13,17] had adduced fairly strong evidence

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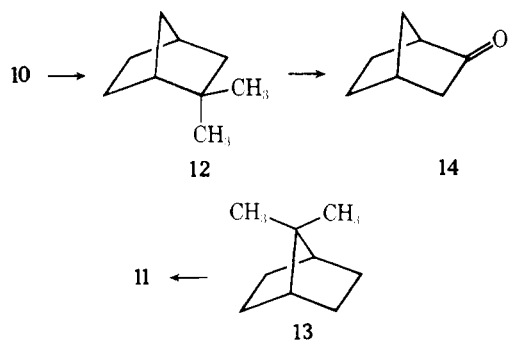
Scheme I



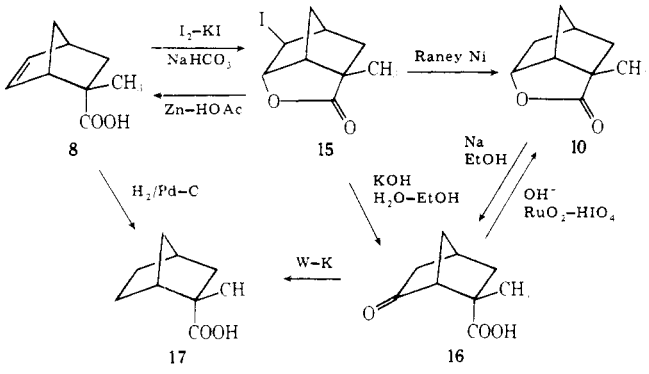
in confirmation of the structures of **10** and **11**, the matter could not be considered as settled, and other structures which fitted the extant data existed as viable alternatives.

This background sets the stage for the present study. These structural questions could only be settled in a rigorous way by extensive chemical degradation, and our approach toward achieving this level of proof is embodied in Scheme I.

Because of the presence of a plane of symmetry in **13** and the absence of this element in **12**, the two compounds are potentially readily distinguishable by NMR. Furthermore 2,2-dimethylnorbornane (**12**) is available by unambiguous synthesis from norbornanone (**14**). As outlined below, the direct conversion of **10** to **12** was not carried out but the structural correlation was achieved between **9** and **12**.

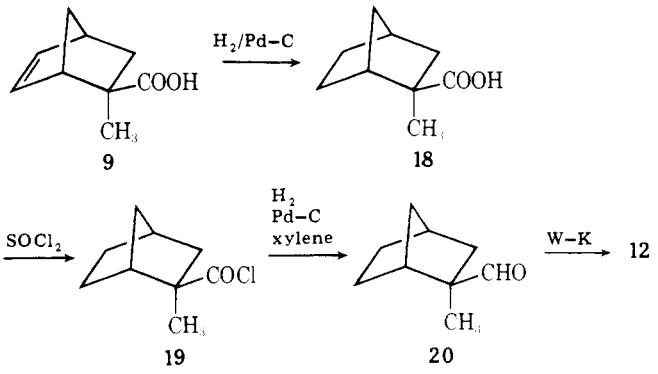
Results and Discussion

Since iodolactonization (**8** → **15**) proceeds without rearrangement as revealed by deiodination with zinc and acetic acid (**15** → **8**),[1] reductive removal of iodine (**15** → **10**) using

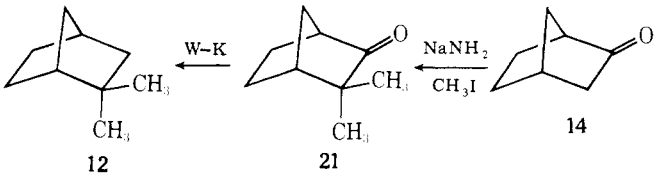


Raney nickel in pyridine established the structure of 6-*endo*-hydroxy-2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid γ-lactone (**10**) as shown. Earlier studies by Ramey et al.[8] on the NMR and IR of **10** also confirm this assignment. Using a method developed by Moriarty et al.[18] for the conversion of lactones to keto acids, namely, ruthenium tetroxide oxidation under basic conditions, **10** was converted smoothly to 2-*exo*-methyl-6-oxobicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**16**). Keto acid **16** was also synthesized by base dehydrohalogenation on iodo lactone 2-*endo*-carboxylic acid γ-lactone **15**. Sodium in ethanol reduction of **16** yielded **10**. Wolff–Kishner reduction of **16** proceeded in high yield to 2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**17**), which was also obtained by catalytic reduction of 2-*exo*-methylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (**8**).

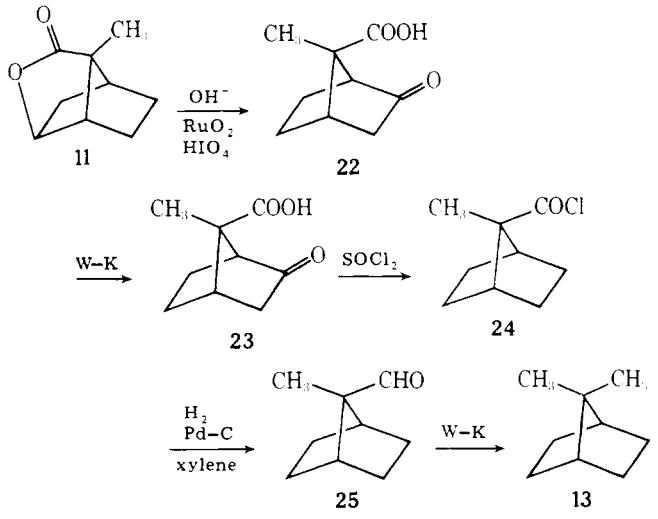
The degradation problem now becomes one of converting the carboxyl group in 2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**17**) or 2-*endo*-methylbicyclo-[2.2.1]heptane-2-*exo*-carboxylic acid (**18**) to a methyl group since both of these structures are established by the above transformations. This was accomplished by formation of 2-



endo-methylbicyclo[2.2.1]heptane-2-*exo*-carboxylic acid chloride (**19**) and catalytic hydrogenation of **19** using palladium on charcoal in *p*-xylene to the aldehyde 2-*endo*-methylbicyclo[2.2.1]heptane-2-*exo*-carboxaldehyde (**20**). Wolff–Kishner reduction of **20** afforded 2,2-dimethylnorbornane (**12**). This compound was synthesized independently by dimethylation of norbornanone (**14** → **21**) and Wolff–Kishner reduction of the carbonyl group (**21** → **12**).



The next objective was the conversion of the rearranged lactone **11** into 7,7-dimethylnorbornane (**13**). Oxidation of 2-*exo*-hydroxy-7-*anti*-methylbicyclo[2.2.1]heptane-7-*syn*-carboxylic acid γ-lactone (**11**) with ruthenium tetroxide under basic conditions yielded keto acid 7-*anti*-methyl-2-oxobicyclo[2.2.1]heptane-7-*syn*-carboxylic acid (**22**). Removal of the keto group by Wolff–Kishner reduction followed by acid chloride formation, catalytic reduction, and a second Wolff–



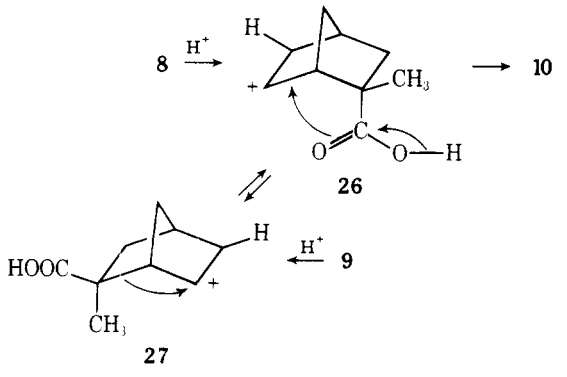
Kishner reduction (**22** → **23** → **24** → **25** → **13**) in a manner analogous to the scheme used in the earlier series afforded 7,7-dimethylnorbornane (**13**).

The NMR spectra of 2,2-dimethyl- and 7,7-dimethylnorbornane shown in Figure 1 (see supplementary material) are in complete agreement with expectation. Without assigning the absorptions to particular protons, the relative simplicity of the spectrum of **13** strongly indicates the presence of a symmetry plane, and by the same token the absence of one in **12**.

This sequence constitutes a rigorous proof of the structures of the two isomeric γ-lactones **10** and **11** and is in agreement

with the original structural assignments of Beckmann and Geiger.[13a] The structure of the hydroxy acid related to **11** has been determined by x-ray diffraction.[13b]

Mechanism of Formation of Lactone. Unrearranged lactone **10** can be visualized as resulting from protonation of the double bond in **8** and intramolecular neutralization of carbocation **26** by the carboxyl group. Wagner–Meerwein



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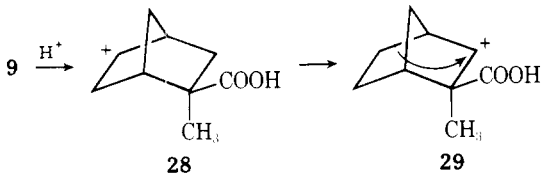
27

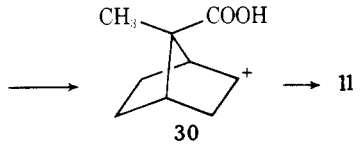
rearrangement of **26** yields carbocation **27**, which is also the same carbocation as is formed by protonation of the exo carboxylic acid **9**.

This offers an intermediate for the equilibration of the two acids.

The most economical route to rearranged lactone **11** is via 1,3-endo hydride shift from carbocation **28** followed by Wagner–Meerwein rearrangement and intramolecular capture of the resulting carbocation (**28** → **29** → **30** → **11**). Two routes



28 **29**



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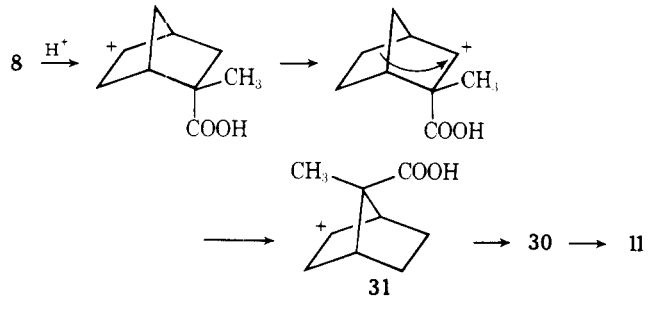
are conceivable for the formation of **11** from the endo acid **8**. Either **8** isomerizes to **9** under the acid conditions, or, alternatively, the above sequence may occur starting from **8** to yield carbocation **31**. A second 1,3-endo hydride shift yields carbocation **30**.



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Experimental Section

General. IR spectra were recorded with a Unicam SP 1000 spectrometer. NMR data were obtained by using Varian Associates T-60A instruments, with Me_4Si as an internal standard. The mass spectra were mesaured with an AEI MS-30 mass spectrometer at an ionizing voltage of 70 eV. VPC analyses were performed on a Hewlett Packard Model 776 instrument. Melting points were taken in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by MicroTech Laboratory, Skokie, Ill. Magnesium sulfate was used as a drying agent.

2-*endo*-Methylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic Acid (9) and 2-*exo*-Methylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic Acid (8). The method of Beckmann, Schaber, and Bamberger[17] was followed. Methacrylic acid (129 g, 1.5 mol) and 116 g (1.9 mol) of freshly distilled cyclopentadiene were kept at reflux on a water bath for 4 h. Distillation gave 91 g of unreacted methyacrylic acid and dicyclopentadiene and 125 g (55%) of **9** and **8**, bp 110 °C (2.5 mm). After recrystallization of the crude product three times from petroleum ether, 106 g (85%) of pure **9** was obtained, mp 82–83 °C (lit. bp 83 °C[17] and mp 79–81 °C[16]). From the mother liquors of **9**, 6.5 g (52%) of **8** was obtained by repeated fractional recrystallization, mp 98–99 °C (lit. bp 109 °C[17] and mp 94–95 °C[16]).

6-*endo*-Hydroxy-5-*exo*-iodo-2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid γ-Lactone (15). The method of van Tamelen and Shamma[23] was followed. A solution of 3.1 g (20 mmol) of **8** in 120 mL of 0.5 N sodium bicarbonate and a solution of 10.1 g (40 mmol) of iodine and 19.9 g (120 mmol) of potassium iodide in 60 mL of water were mixed together and allowed to stand in the dark for 24 h. The resulting dark oily precipitate which separated was taken up in chloroform and shaken with aqueous sodium thiosulfate until colorless. The aqueous layer was extracted with chloroform, and the extracts were washed with aqueous thiosulfate until colorless. The combined chloroform extracts were washed successively with aqueous sodium bicarbonate and water. They were dried over anhydrous magnesium sulfate and filtered, and the chloroform was removed on a rotavapor. The resulting residue was recrystallized from ethanol–petroleum ether to yield 4.3 g (80%) of **15**, mp 84.5–85.5 °C (lit.[16] mp 83–86 °C).

2-*exo*-Methyl-6-oxobicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid (16). (a) From 6-*endo*-Hydroxy-5-iodo-2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid γ-Lactone (15). The method of Meek and Trapp[16] was used. Compound **15** (3.3 g, 12 mmol) was added to a solution of 6 g (107 mmol) of potassium hydroxide in 90 mL of water and 90 mL of 95% ethanol and heated on a steam bath for 1 h. The solution was cooled, filtered, acidified with dilute hydrochloric acid, and extracted with ether. The ether extracts were washed with sodium bicarbonate solution and water and dried over sodium sulfate. After filtration, the ether was removed on a rotavapor and the residue was crystallized from acetone to give 1.5 g (75%) of **16**, mp 129–130 °C (lit.[13,16] mp 129–130 °C).

(b) From 6-*endo*-Hydroxy-2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid γ-Lactone (10). The method of Gopal, Adams, and Moriarty[18] was used. A 2-g (13-mmol) amount of **10** was added to 26.5 mL of 0.498 N sodium hydroxide. The mixture was heated on a water bath until a homogeneous solution was obtained. It was then cooled to room temperature, and two drops of phenolphthalein solution was added. Excess base was neutralized with dilute hydrochloric acid solution. To the neutral aqueous solution of sodium salt of the hydroxy acid was added 20 mg of ruthenium dioxide. The solution was vigorously stirred while a solution containing 4.83 g (14 mmol) of sodium periodate was added dropwise. The solution developed a yellow color, indicating the presence of ruthenium tetroxide. After total addition of sodium periodate solution, the excess ruthenium tetroxide was destroyed with isopropyl alcohol. The solution was acidified and extracted with five 100-mL portions of ethyl acetate. The combined extracts were dried over magnesium sulfate and filtered, and the solvent was removed on a rotavapor. The crystalline residue was recrystallized from acetone to yield 1.7 g (85%), mp 129–130 °C (lit.[13,16] mp 129–130 °C).

6-*endo*-Hydroxy-2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid γ-Lactone (10). (a) From 2-*exo*-Methyl-6-oxobicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid (16). The method of Beckmann and Geiger[13] was followed. A 1.2-g (71-mmol) amount of **16** was dissolved in 30 mL of absolute ethanol and heated to reflux. Then 2.4 g (104 mmol) of sodium was added over a period of 1 h. The solution was cooled and poured into 100 mL of water. It was then extracted with ether three times. The extracts were dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting oily residue was chromatographed on silica gel. Elution with 40% ether–pentane gave 0.4 g (37%) of **10** as a pale yellow solid, mp 63–65 °C. Recrystallization from pentane raised the melting point to 64–65 °C (lit.[13] mp 64–65 °C).

(b) From the Lactone of 6-*endo*-Hydroxy-5-iodo-2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid (15). A 500-mg amount of **15**, 3.1 g of dry pyridine, and 9.3 g of Raney nickel (no. 28, W. R. Grace & Co.) were added to 100 mL of absolute ethanol. The mixture was shaken mechanically for 24 h under 30 psi of hydrogen pressure. The mixture was filtered, and the Raney nickel was destroyed carefully with dilute hydrochloric acid solution. Most of the alcohol was removed on a rotavapor, and the residue was dissolved

into 100 mL of ether. The ether solution was washed with dilute hydrochloric acid solution and 10% sodium bicarbonate solution and dried with anhydrous magnesium sulfate. The ether was removed, and the residue was recrystallized from ether–pentane to yield 0.23 g (85%) of **10**, mp 64–65 °C (lit.[13] mp 64–65 °C).

2-*exo*-Hydroxy-7-*anti*-methylbicyclo[2.2.1]heptane-7-*syn*-carboxylic Acid γ-Lactone (11). The method of Beckmann and Geiger[13] was followed. A 12-g (80-mmol) amount of **9** was stirred with 100 mL of 75 vol % sulfuric acid for 18 h at room temperature. The solution was poured into 1000 g of ice water. The white precipitate was extracted with ether several times. The ether extracts were dried over anhydrous magnesium sulfate, and the solvent was removed on the rotavapor. The residue was recrystallized from ethanol to yield 9.9 g (85%) of **11**, mp 124.5–126 °C (lit.[13] mp 125–126 °C).

2-*endo*-Methylbicyclo[2.2.1]heptane-2-*exo*-carboxylic Acid (18). Compound **9** (15.2 g) was dissolved in 200 mL of methanol, and a small amount of Pd–C catalyst was added. The solution was shaken mechanically for 24 h under 30 psi of hydrogen. The reaction mixture was filtered, and the methanol was removed on a rotavapor. The residue was distilled at 114.5–115 °C (1.5 mm) to give 13.9 g (90%) of **18**. The distillate solidified after standing at room temperature: mp 27–27.5 °C, IR (CCl_4) 1715 cm^{-1} (C=O stretching); NMR (CCl_4) δ 1.26 (s, 3 H, methyl), 1.27–2.62 (m, 10 H). Anal. Calcd for $C_9H_{14}O_2$: C, 70.13; H, 9.09. Found: C, 70.23; H, 9.35.

2-*endo*-Methylbicyclo[2.2.1]heptane-2-*exo*-carboxaldehyde (20). The method of Asahina, Ishidate, and Sano[20] was followed. A mixture of 8.6 g (50 mmol) of **19**, 120 mL of freshly distilled *p*-xylene, and 1.5 g of Pd–C was refluxed for 12 h with hydrogen passing through it. The mixture was cooled and filtered, and the solvent was removed by simple distillation. The residue was filtered over silica gel to remove any trace of *p*-xylene. The product was distilled at 43–44 °C (0.9 mm) to yield 5.0 g (73%) of **20**: IR (neat) 1736 cm^{-1} (C=O stretching); NMR (CCl_4) δ 1.10 (s, 3 H, methyl), 8.99 (s, 1 H, –CHO), 1.11–2.80 (m, 10 H). Anal. Calcd for $C_9H_{14}O$: C, 78.23; H, 10.14. Found: C, 78.19; H, 9.98.

2,2-Dimethylnorcamphor (21). Essentially, the method of Corey, Hartmann, and Vatakencherry was used.[21] Norbornanone (**14**; 12 g, 0.1 mol) and 0.25 mol (9.8 g) of sodium amide were refluxed in ether under high speed stirring with the passage of a stream of nitrogen through the reaction vessel to expel ammonia. Vigorous stirring and small particle size of the sodium amide are essential to minimize aldol condensation and raise the yield of **21**.

Methyl iodide (1 mol) in a small amount of ether was added dropwise to the reaction mixture after 0.05 mol of ammonia had been expelled by flushing with nitrogen. (The expelled ammonia was led into a solution of 0.1 N HCl.) The mixture was subsequently kept at reflux until evolution of ammonia had ceased. The mixture was cooled to room temperature and added carefully to 500 mL of water to destroy excess sodium amide. The aqueous reaction mixture was extracted with ether several times. The ether extracts were dried over magnesium sulfate and concentrated to dryness. The residue was distilled to yield 6.1 g (47%) of **21**, bp 68–69 °C (2.0 mm). IR and NMR spectra were identical with those reported.[22]

2,2-Dimethylnorbornane (12). (a) From 2-*endo*-Methylbicyclo[2.2.1]heptane-2-*exo*-carboxaldehyde (20). A mixture of 5.5 g (40 mmol) of **20**, 5.5 g (150 mmol) of 95% of hydrazine hydrate, 7.5 g (134 mmol) of potassium hydroxide, and 50 mL of diethylene glycol in a 100-mL flask was distilled through a 10-cm Vigreux column at 200 °C over a period of 2 h. The distillate was taken up in ether and washed with dilute hydrochloric acid solution and water. The ether was removed, and the residue was distilled at 142–143 °C to give 1.9 g (39%) of **12**: IR (neat), no carbonyl absorption; NMR (CCl_4) δ 0.96, 0.93 (2s, 6 H, two methyl), 1.10–2.26 (m, 10 H, all other hydrogens). Anal. Calcd for C_9H_{16}: C, 87.10; H, 12.90. Found: C, 87.01; H, 12.86.

(b) From 2,2-Dimethylnorcamphor (21). The Wolff–Kishner reduction was used. A 55-g amount of **21** was treated with 5.5 g of hydrazine hydrate and 7.5 g of potasium hydroxide in 50 mL of diethylene glycol. Using the same workup procedure described above yielded 2.5 g (51%) of **12**. The IR and NMR spectra were identical with those of the sample prepared from 2-*endo*-methylbicyclo[2.2.1]heptane-2-*exo*-carboxaldehyde (**20**). Mass spectrum: parent peak at *m/e* 124.

7-*anti*-Methyl-2-oxobicyclo[2.2.1]heptane-7-*syn*-carboxylic Acid (22). The method of Gopal, Adams, and Moriarty[18] was used. An 8-g (53-mmol) amount of **11** was added to 106 mL of 0.5 N sodium hydroxide. The mixture was heated on a water bath until a homogeneous solution resulted. The solution was then cooled to room temperature, and two drops of phenolphthalein solution were added. Excess base was neutralized with dilute hydrochloric acid. To the neutral aqueous solution of the sodium salt of the hydroxy acid was added 50 mg of ruthenium dioxide. The solution was vigorously stirred while a few drops of solution containing 11.3 g (53 mmol) of sodium periodate were added. The solution developed a yellow color, indicating the presence of ruthenium tetroxide. Upon appearance of a black precipitate, dropwise addition of the sodium periodate was continued. After addition of the sodium periodate solution, excess ruthenium tetroxide was destroyed with isopropyl alcohol. The solution was acidified and extracted with five 100-mL portions of ethyl acetate. The extracts were combined and dried, and the solvent was removed on a rotavapor. The crystalline residue was recrystallized from acetone to yield 7.6 g (94%) of **22**, mp 207–208 °C (lit.[13] mp 206–208 °C).

7-Methylbicyclo[2.2.1]heptane-7-carboxylic Acid (23). The Wolff–Kishner reduction was used. A mixture of 8.92 g (54 mmol) of **22** and 11 g (300 mmol) of 95% hydrazine hydrate was added to a solution prepared from 15 g of sodium and 300 mL of diethylene glycol.[19] The reaction mixture was kept at reflux for 50 h. At the end of this time it was cooled to room temperature, diluted with water, and acidified with dilute hydrochloric acid solution. The precipitate which formed was filtered, washed with water, taken up in ether, and dried over magnesium sulfate. The solvent was removed on a rotavapor. The crystalline residue was recrystallized from acetonitrile to yield 4.6 g (52%) of **23**, mp 194–195 °C (lit.[13] mp 194–195 °C).

7-Methylbicyclo[2.2.1]heptane-7-carboxylic Acid Chloride (24). The same method as for compound **19** was employed. A 6.2-g amount of **23** gave 5.9 g (85%) of **24**. The product was purified by sublimation: mp 67–68 °C; IR (CCl_4) 1800 cm^{-1} (C=O stretching); NMR (CCl_4) δ 1.42 (s, 3 H, methyl), 1.15–2.40 (m, 10 H).

7-Methylbicyclo[2.2.1]heptane-7-carboxaldehyde (25). The method employed for the synthesis of compound **20** was used. An 8.6-g amount of **24** gave 4.4 g (65%) of **25**. The product was filtered through a silica gel column and purified by sublimation: mp 112–114 °C; IR (CCl_4) 1738 cm^{-1} (C=O stretching); NMR (CCl_4) δ 1.34 (s, 3 H, methyl), 9.24 (s, 1 H, –CHO), 1.14–2.25 (m, 10 H). Anal. Calcd for $C_9H_{14}O$: C, 78.23; H, 10.14. Found: C, 78.07; H, 9.98.

7,7-Dimethylnorbornane (13). The same method used for compound **12** was followed. A 2.8-g amount of **25** gave 1.1 g (43%) of **13**. The product was purified by sublimation: mp 86–87 °C; IR (CCl_4), no carbonyl group; NMR (CCl_4) δ 0.98 (s, 6 H, two methyl), 1.05–2.04 (m, 10 H). Anal. Calcd for C_9H_{16}: C, 87.10; H, 12.90. Found: C, 87.04; H, 12.88.

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Supplementary Material Available: NMR spectra (Figure 1) of 7,7-dimethylnorbornane and 2,2-dimethylnorbornane (1 page). Ordering of information is given on any current masthead page.

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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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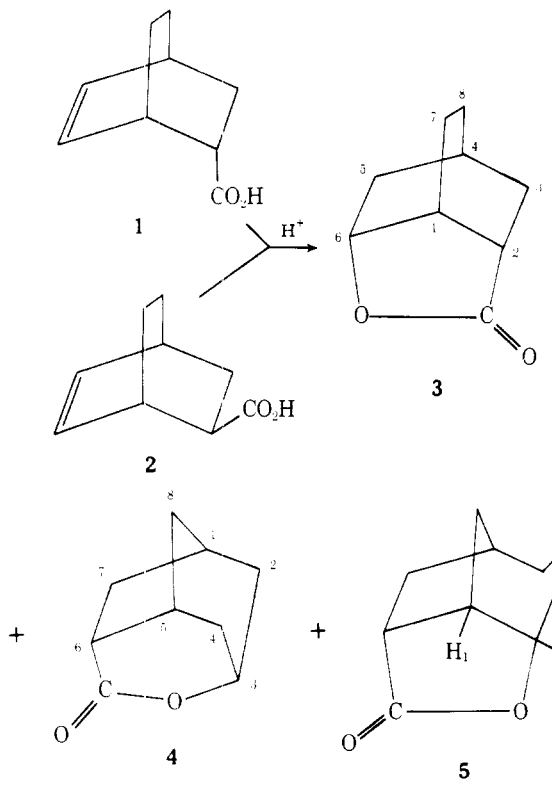
The structures of the γ- and δ-lactones obtained in the acid-catalyzed cyclization of bicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic acid have been established. By means of chemical degradation the lactones were proven to be 6-*endo*-hydroxybicyclo[2.2.2]octane-2-*endo*-carboxylic acid γ-lactone, 3(a)-hydroxybicyclo[3.2.1]octane-6-*endo*-carboxylic 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.

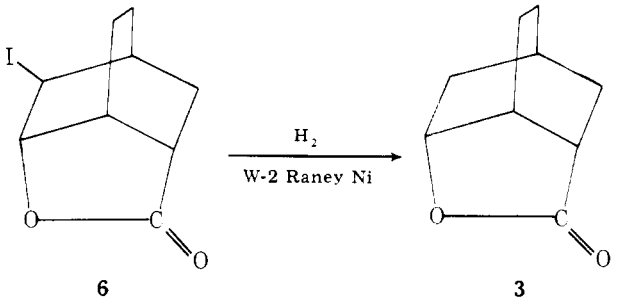
In the preceding paper we discussed the rearrangements which may occur upon acid-catalyzed intramolecular lactone formation in the *exo*- and *endo*-2-methylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acids.[1-3] Analogous cationic rearrangements also are observed in the bicyclo[2.2.2]octyl system.

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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