Registry No.—1-OH, 60595-08-6; 2-OH, 60595-09-7; 7-OH, 694-70-2; 11, 53585-67-4; tricyclo[4.1.0.0^{2,7}]hept-3-one, 37939-70-1; *p*-nitrobenzoyl chloride, 122-04-3.

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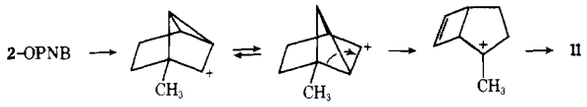
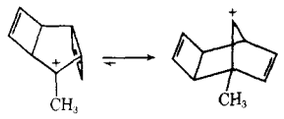


However, if this mechanism is involved in the hydrolysis of **2**-OPNB, methylnorbornenol would be expected to be a major product (but is not), since a great difference in the stability between the following carbonium ions has been reported.[9]



Thus, we prefer the above mechanism to this alternate one.

(7) Melting points were taken on a Yamato MP-21 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Shimadzu IR-400 spectrophotometer and ultraviolet spectra were determined with a Shimadzu UV-200 spectrophotometer. Nuclear magnetic resonance spectra were recorded using a Hitachi R-24 instrument with chemical shift (δ) given in parts per million downfield from Me_4Si. Gas–liquid chromatography was performed on a Shimadzu GC-4B instrument. Microanalyses were determined in the microanalytical laboratory of the Institute of Physical and Chemical Research, Wako-shi, Saitama, Japan.

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The Role of the Generalized Anomeric Effect in the Conformational Analysis of 1,3-Dioxacycloalkanes. Conformational Analysis of 3,5-Dioxabicyclo[5.1.0]octanes and 3,5,8-Trioxabicyclo[5.1.0]octanes

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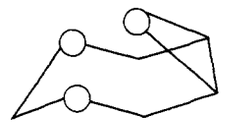
Conformational analysis of 1,3-dioxacycloalkanes has received considerable attention.[1-5] Equilibrium studies on substituted 1,3-dioxacyclopentanes and 1,3-dioxacycloheptanes indicate that numerous low-energy chair conformations, which are interconnected by pseudorotational pathways, are available to an equilibrating pair of diastereoisomers. In contrast 1,3-dioxacyclohexane has only one favorable low-energy chair conformation for each isomer of a cis–trans pair.

Examination of models of 1,3-dioxacycloheptanes reveals that when pseudorotation at C-5,6 is prohibited, only one chair conformation is possible. The pseudorotation pathway of the chair form may be excluded by introduction of a double bond at C-5,6 or by construction of a small ring containing C-5 and C-6. Studies of the conformations for compounds which contain a double bond at C-5,6 indicate that 2,2-dimethyl-1,3-dioxa-5,6-benzocycloheptene,[6] *cis*- and *trans*-4,7-dimethyl-1,3-dioxacycloheptene-5-ene, and *r*-2-*tert*-butyl-*c*-4,*t*-7-dimethyl-1,3-dioxacycloheptene-5-ene[5] exist in twist-boat conformations.

Our interest in twist-boat conformations in the 1,3-dioxacycloheptene-5-enes has led to an investigation of the effect that the construction of a small ring would have on the conformation of these compounds. Recent reports that cycloheptene oxide[7] exists in an equilibrium of two chair conformations and that cycloheptene is also in a chair conformation are of special interest. The conformation of 1,3-dioxacycloheptene-5-ene is unsettled.[8] Low-temperature proton magnetic resonance studies failed to indicate line broadening at −120 °C. However, carbon-13 magnetic resonance data strongly suggests that 2,2-dimethyl-1,3-dioxacycloheptene-5-ene is in a twist-boat conformation.[5]

It is evident that the epoxide ring does not impart sufficient strain to force cycloheptene oxide into a twist form nor does the double bond make the twist form the more stable conformer for cycloheptene. It seemed probable that 3,5,8-trioxabicyclo[5.1.0]octane (1,3-dioxacycloheptene-5-ene oxide) might be more stable in a twist-boat than in a chair conformation. In addition to the strain provided by the epoxide ring an unfavorable interaction due to an anomeric effect[9] could be anticipated for chair conformations **1** and **3** which is relieved in the twist-boat conformation **2.**



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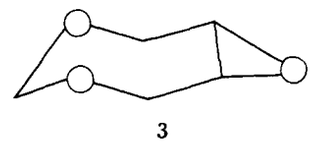

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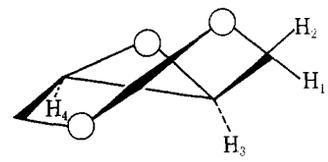

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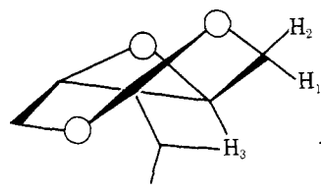

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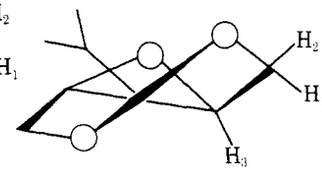

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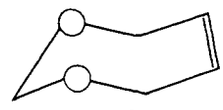


6

The 1,3-dioxacycloheptene-5-ene oxide was synthesized by epoxidation of 1,3-dioxacycloheptene-5-ene with *m*-chloroperbenzoic acid. The proton magnetic resonance spectrum of this compound remained unchanged in the temperature range 30 to −160 °C. This fact suggested that this molecule might indeed be in a twist-boat conformation. However, it is possible that the coalescence temperature is below −160 °C and that the compound exists as an equilibrium of conformations **1** and **3.**

Supporting evidence for a twist-boat conformation comes from coupling constants for *exo*- and *endo*-2-isopropyl-1,3-dioxacycloheptene-5-ene oxide, **4** and **5**, respectively. The endo isomer gave the following coupling constants: $J_{1,2}$ (−13.67),

$J_{1,3}$ (3.78), $J_{2,3}$ (3.79), and $J_{3,4}$ (6.93). The exo isomer gave the following coupling constants: $J_{1,2}$ (−13.99), $J_{1,3}$ (1.13), $J_{2,3}$ (2.99), and $J_{3,4}$ (8.00). Values calculated from the Karplus equation for the chair conformation of the exo isomer with dihedral angles of approximately 155 and 37° were 11 and 7.6 Hz, respectively. Values calculated for the chair conformation of the endo isomer with dihedral angles of approximately 90 and 25° were 2 and 9.3 Hz.[10] It is evident that the experimental values best describe a twist-boat conformation.

Both spectra show evidence of virtual coupling. The spectra were readily reproduced using a LAOCOON III program. The configurational assignments were made on the basis of the chemical shift for the C-2 proton. In the exo isomer this proton lies in the face of the epoxide ring and is expected to give an absorption further upfield than the corresponding proton in the endo isomer. Accordingly that isomer with the C-2 proton chemical shift at 385 Hz was assigned the exo configuration and the isomer with the C-2 proton chemical shift at 411 Hz was assigned the endo configuration.

The construction of the small ring at C(5,6) makes 1,3-dioxacyclohept-5-ene oxide more stable in the twist-boat conformation than in the chair conformation. It is suggested that a combination of the generalized anomeric effect[9] and the strain imposed on the system by the double bond or the epoxide ring results in higher energies for the chair conformations than for the twist-boat conformations.

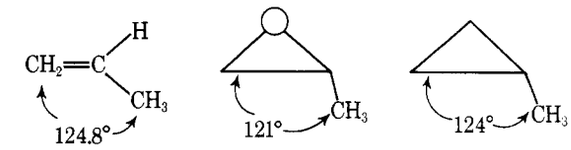
The geometry of the chair conformations for the 1,3-dioxacyclohept-5-enes (**6**) is such that the C_4–O and the C_7–O bonds are syn periplanar and each of these bonds is in turn syn (and anti) periplanar to the p orbitals of the π bonds. In the twist-boat conformations these bonds and the p orbitals are all oriented gauche. These conformations are predicted by the Wolfe rule which states[11] "When electrons pairs or polar bonds are placed on adjacent pyramidal atoms, syn or anti periplanar orientations are disfavored with respect to that structure which contains the maximum number of gauche interactions".

The geometry of the epoxide molecules is such that the two chair conformations (**1** and **3**) have C_4–O and C_7–O bonds which are syn periplanar. Conformation **1** has the C_4–O (C_7–O) bonds and the C_5–O (C_6–O) epoxide bonds very close to syn periplanar.

Conformation **3** has the C_4–O (C_7–O) bonds and the C_5–O (C_6–O) epoxide bonds very close to anti periplanar. These bonds are all oriented gauche to each other in the twist-boat conformation (**2**). This again is consistent with the Wolfe rule.

The reports that cycloheptene[12] and cycloheptene oxide are more stable in chair than in twist-boat conformations indicate that the strain imposed by the double bond or the epoxide ring is not sufficient to raise the energy of the chair conformation above that of the twist-boat. It appears that an additional amount of energy is required to accomplish this, as indicated for the 1,3-dioxacyclohept-5-enes and the 1,3-dioxacyclohept-5-ene oxides. The question remains as to whether the generalized anomeric effect from the 1,3 oxygens alone is sufficient for this purpose or if a more encompassing interaction, as described above, is required.

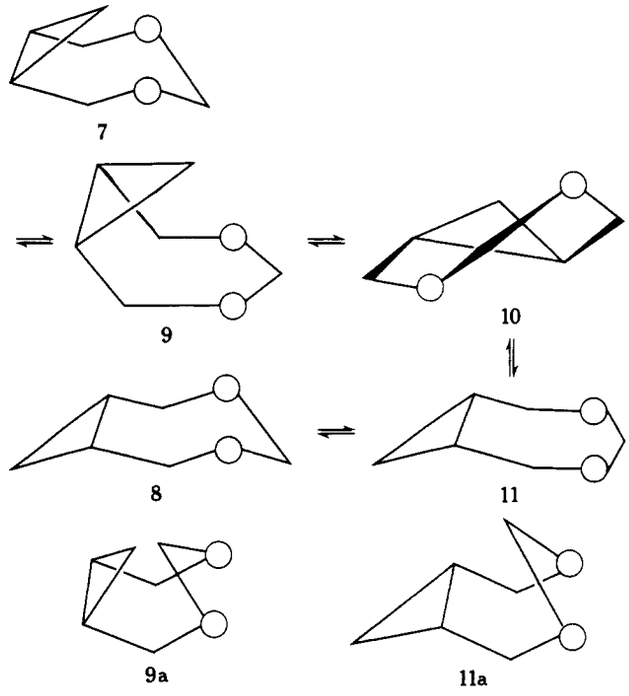
To shed some light on this point we have studied the conformation of 3,5-dioxabicyclo[5.1.0]octane. This molecule has a 1,3-generalized anomeric effect and a source of strain imposed by the cyclopropyl ring. There is, however, no extended generalized anomeric effect. The strain imposed by the cyclopropyl ring is probably not too different from that imposed by the double bonds or the epoxide ring. The values for the bond angles for propylene oxide,[13] propene,[14] and methylcyclopropane[15] are shown below and indicate that the strain created in the corresponding seven-membered rings by bond angle deformation should be similar.



Low temperature proton magnetic resonance spectra indicate that 3,5-dioxabicyclo[5.1.0]octane exists as a mixture of two conformations (**7** and **8**). It appears that the 1,3-generalized anomeric effect is not of sufficient strength to raise the energy of the chair conformation above that of the twist-boat conformation and that the more generalized anomeric effect is required.

^{1}H NMR Studies. The ^{1}H NMR spectrum at 30° for 3,5-dioxabicyclo[5.1.0]octane gives an AB pattern for the C(4) protons. The chemical shifts are 4.79 and 4.60 ppm downfield from Me_4Si in deuterioacetone solution. At lower temperatures the lines broadened until at −55 °C the spectrum was flat, indicating that the coalescence temperature, T_c, had been reached. At −90 °C the AB pattern had changed into two distinct AX patterns. The chemical shift difference between the averaged chemical shifts of the AX patterns was 34 Hz. An activation energy of 10.7 kcal/mol is calculated from the equation[16] $\Delta G^{\ddagger} = RT_c \ln (2KT_c/h\pi\Delta\delta)$.

This value is larger than the value for cycloheptene oxide (7.9 kcal/mol). Of the possible pathways that can be drawn for the interconversion of the two chair forms, the one that is most attractive is indicated below.



The boat conformations are probably energy maxima for the conversion **9** ⇌ **10**, **10** ⇌ **11**. Dreiding models show that for conformation **9a** the C(4) and C(8) endo hydrogens are in contact position and should represent a very high point on the energy curve. Conformation **11a** is analogous to the boat form of cycloheptene, which has been suggested as an energy maximum rather than a local minimum for that conversion process.[17] The interaction between the C(5,6) bond and the C(4) hydrogen should be more severe in this compound than in cycloheptene because the C–O bond distance is shorter than the C–C bond distance. Conformation **9a** is probably a very close representation of the transition state for the process **9** ⇌ **10**.

Conformations **9** and **11** are such that C(2), C(4), C(6), O(3), and O(5) are in a plane. Since there are no hydrogens in the 3 and 5 positions, the unfavorable energy due to eclipsed hy-

drogens is avoided. This is in contrast to the process suggested for cycloheptene oxide where the conformations analogous to **9** and **11** have six eclipsed hydrogens.

***exo*- and *endo*-4-Isopropyl-3,5-dioxabicyclo[5.1.0]-octanes.** Configurational assignments were made on the basis of coupling constants for the C(1) and C(2) hydrogens and the chemical shift of the C(4) hydrogens. The coupling constants were readily ascertained from the spectra of the pure isomers. The isopropyl group is an effective conformational bias and there was no indication of any conformer other than the indicated chair.

The endo isomer gave coupling constants of $J_{2a-1e} = 1.3$, $J_{2e-1e} = 12.1$, and $J_{2a-2e} = -12.5$ Hz. These values are consistent with values calculated for dihedral angles of 90 and 25°. The exo isomer gave coupling constants of $J_{2a-1a} = 10.0$, $J_{2e-1a} = 6.7$, and $J_{2a-2e} = -12.0$ Hz. These values are consistent with calculated values for dihedral angles of approximately 155 and 37°.

The chemical shift data for the C(2) hydrogens are of special interest. For the endo isomer the C(2a) hydrogen absorption is downfield from that of the C(2e) hydrogen, whereas in the exo isomer the C(2e) hydrogen absorbs downfield from that of the C(2a) hydrogen. The cyclopropyl ring shields the 2a hydrogen more in the exo isomer than in the endo isomer. This is consistent with the configurational assignment since the 2a hydrogen lies in the face of the ring in the endo isomer.

The shielding ability of the cyclopropyl ring provides the basis for the assignment of the axial and equatorial hydrogens at C(4) for the low temperature spectra of 3,5-dioxabicyclo[5.1.0]octane. For conformer **8** the hydrogen which lies in the face of the cyclopropyl ring is axial and is assigned the lower chemical shift value (3.92 ppm); for conformer **7** the equatorial hydrogen is assigned to the 5.14 ppm chemical shift. These assignments are consistent with the fact that equatorial hydrogens absorb at lower field than axial hydrogens in the cyclohexanes.

Equilibration. The *exo*- and *endo*-4-isopropyl-3,5-dioxabicyclo[5.1.0]octanes were equilibrated in refluxing benzene with catalytic amounts of *p*-toluenesulfonic acid. The equilibrium was approached from both sides using samples enriched in one isomer. The ratio endo/exo was 1.2/1 ± 0.03 corresponding to $-\Delta G^{\ddagger} = 0.12$ kcal/mol.

Experimental Section

^{1}H NMR spectra were recorded on a Varian A-60A NMR spectrometer. The low temperature spectra were recorded on a Varian HA 100D spectrometer. Samples were run in deuterioacetone as 10% solutions. All chemical shifts are reported in parts per million downfield from internal Me_4Si. The carbon-13 spectra were recorded at 25.15 MHz on a Varian HA 110D NMR spectrometer interfaced with a Digilab NMR-FTS-3 pulse and data system. The number of data points was 8K or 16K as required to obtain satisfactory resolution. Spectra were recorded with broad band proton decoupling. All chemical shifts are referenced to internal Me_4Si and reported in parts per million. All mass spectra were determined on a AEI-9 high-resolution mass spectrometer. The infrared spectra were recorded on a Beckman IR-8 instrument and the absorption values are reported in microns. *cis*-1,2-Cyclopropanedimethanol was prepared as described in the literature.[18] 1,3-Dioxacyclohept-5-ene and 2-isopropyl-1,3-dioxacyclohept-5-ene were prepared as described in the literature.[19]

3,5-Dioxabicyclo[5.1.0]octane. The general procedure for the preparation of these compounds is that of Bannock and Lappin.[16] The preparation of 3,5-dioxabicyclo[5.1.0]octane is described as a representative example. A mixture of 9.6 g (0.94 mol) of *cis*-1,2-cyclopropanedimethanol, 3.0 g (0.10 mol) of paraformaldehyde, 50 mg of *p*-toluenesulfonic acid, and 100 ml of benzene was refluxed using a Dean-Stark distillation trap. The reaction was terminated when 0.1 mol of water was collected. The mixture was distilled under vacuum and the fraction boiling at 79–81°C (22 Torr) was collected. The yield was 6.1 g (55%): IR (neat) 3.40, 3.50, 6.80, 7.35, 8.70, and 9.20 μ; ^{1}H NMR HC(1,7) 1.30, HC(2,6) 4.28, 3.82, HC(4) 4.79, 4.60, HC(8) 0.80; *m/e* 114 (parent peak); ^{13}C NMR C(1,7) 17.98, C(2,6) 71.55, C(4) 100.59, and C(8) 7.04. The chemical shift values at −90 °C are assigned as follows: CH_a(2,6) 4.22, CH_e(2,6) 3.82, CH_e (4) 5.14, CH_a (4) 4.44 for the conformer **7**. The values for conformer **8** are CH_a (2,6) 3.28, CH_e (2,6) 4.45, CH_a (4) 3.92, CH_e (4) 4.96. The coupling constants for the *endo*- and *exo*-4-isopropyl derivatives are duplicated in the low temperature spectra.

4-Isopropyl-3,5-dioxabicyclo[5.1.0]octanes. The mixture of endo and exo isomers was prepared in 39% yield by reaction of *cis*-1,2-cyclopropanedimethanol and isobutyraldehyde, bp 89–91 °C (22 Torr). The isomers were separated by GLC (8 ft 10% silicone gum rubber, Chromosorb W) and the endo isomer was the first peak: ^{1}H NMR CH_a (2,6) 4.17, CH_e (2,6) 3.85, CH(4) 3.57, C(methyl) 0.88, CH(isopropyl) 1.58; ^{13}C NMR C(4) 114.63, C(2,6) 73.66, C(1,7) 17.45, C(8) 0.85, C(methyl) 16.87, and C(isopropyl) 33.32.

The exo isomer[20] was the second peak: *m/e* 156 (parent peak); ^{1}H NMR CH_a (2,6) 3.10, CH_e (2,6) 4.42, CH(4) 4.10, C(methyl) 0.83, and CH(isopropyl) 1.57; ^{13}C NMR C(4) 112.63, C(2,6) 27.88, C(1,7) 18.39, C(8) 0.58, C(methyl) 17.61, and C(isopropyl) 33.32. The ratio of the areas of the first to the second peak was 1.2/1. Equilibration in refluxing benzene with *p*-toluenesulfonic acid gave the same result.

1,3-Dioxacyclohept-5-ene Oxide. A mixture of 18 g (0.18 mol) of 1,3-dioxacyclohept-5-ene and 40 g (0.23 mol) of *m*-chloroperbenzoic acid in 300 ml of methylene chloride was heated at 40 °C for 96 h. The solution was then cooled and washed with 100 ml of 10% sodium bisulfite solution. The solution was then washed with 5% sodium bicarbonate until all traces of acid were removed. The methylene chloride was evaporated under reduced pressure and the solid that remained was recrystallized from petroleum ether. The yield was 45%; mp 57–58 °C; IR 3.29, 3.35, 3.45, 6.90, 8.40, 9.00, 11.30, 11.50, and 13.75 μ; ^{1}H NMR CH(2) 4.39, 4.76, CH(4,7) 4.06, 4.00, CH(5,6) 4.13; ^{13}C NMR C(2) 97.24, C(4,7) 66.42, C(5,6) 56.47 ppm.

2-Isopropyl-1,3-dioxacyclohept-5-ene Oxide. The procedure for the preparation of this compound was identical with the one described above except that 2-isopropyl-1,3-dioxacyclohept-5-ene was used. The mixture of endo and exo isomers was isolated in 70% yield. The isomers were separated by GLC [12 ft, 5% 1,2,3-tris(cyanoethoxy)propane on Chromosorb]. The first peak was the endo isomer: mp 23–24 °C; ^{1}H NMR CH(2) 4.11, CH(4,7) 4.22, 3.66, CH(5,6) 3.17, CH(isopropyl) 1.79, and CH_3(isopropyl) 0.83; ^{13}C NMR C(2) 110.40, C(4,7) 65.22, and C(5,6) 55.96, C(tertiary isopropyl) 30.98 and C(methyl) 17.88 ppm; IR 3.28, 3.35, 3.45, 6.95, 8.50, 9.10, and 11.30 μ. The exo isomer was the second peak: mp 51–52 °C; ^{1}H NMR CH(2) 3.85, CH(4,7) 4.23, 3.91, CH(5,6) 3.09, CH(isopropyl) 1.68, and CH_3(isopropyl) 0.82; ^{13}C NMR C(2) 110.87, C(4.7) 65.73, C(5,6) 56.61, C(tertiary isopropyl) 32.74, and C(methyl) 17.56 ppm.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also wish to thank Dr. C. D. Schaeffer, Jr., for the low temperature ^{1}H NMR spectra.

Registry No.—3,5-Dioxabicyclo[5.1.0]octane, 25399-19-3; *cis*-cyclopropanedimethanol, 2345-68-8; paraformaldehyde, 30525-89-4; *endo*-4-isopropyl-3,5-dioxabicyclo[5.1.0]octane, 60595-10-0; *exo*-4-isopropyl-3,5-dioxabicyclo[5.1.0]octane, 60619-53-6; 1,3-dioxacyclohept-5-ene oxide, 286-48-6; 1,3-dioxacyclohept-5-ene, 5417-32-3; 2-isopropyl-1,3-dioxacyclohept-5-ene, 5417-35-6; *endo*-2-isopropyl-1,3-dioxacyclohept-5-ene oxide, 60595-11-1; *exo*-2-isopropyl-1,3-dioxacyclohept-5-ene oxide, 60619-54-7.

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(20) The C_2 portion of the hydrogen spectrum was readily duplicated using a LAOCOON III program.

Metal Hydride Reduction of Bicyclo[2.2.2]octan-2-ones. Preparation and Stereochemistry of 5-Substituted Bicyclo[2.2.2]octan-2-ols

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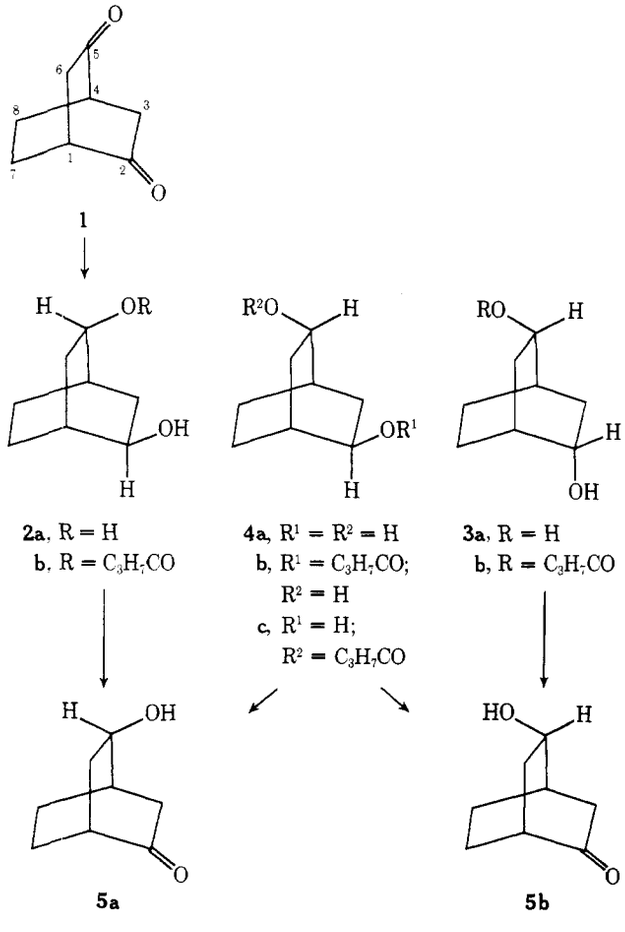
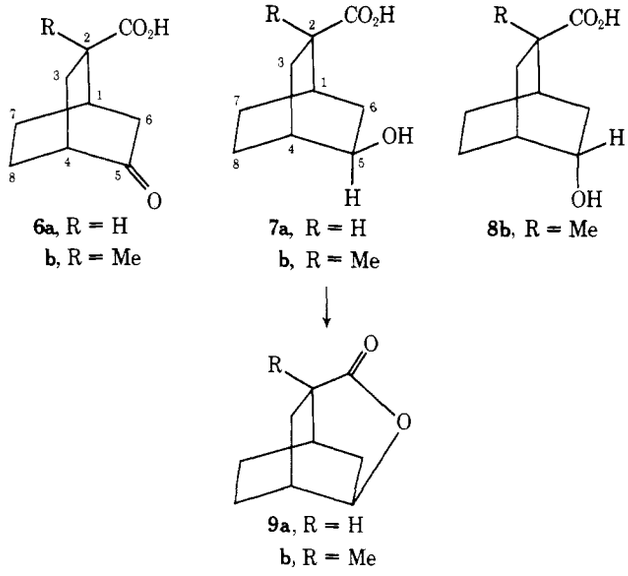
We have examined the metal hydride reduction of a number of 5-substituted bicyclo[2.2.2]octan-2-ones in order to prepare compounds of known relative geometry at the 2,5 position which were required as template molecules for enzyme mimetic studies. Bicyclo[2.2.2]octane-2,5-dione (**1**), prepared by a modification of the method of Guha and Krishnamurthy,[1] was treated with sodium borohydride at room temperature to give a mixture (70–80%) of diols. One isomer could be separated by thin layer chromatography on silica gel, but more satisfactory separation was achieved by either short path column chromatography on alumina[2] or high-pressure liquid chromatography on Porasil. The three diols **2a, 3a,** and **4a** were eluted in that order. The diol **4a** was readily recognized to have the syn-anti configuration of the OH groups, since on partial oxidation it gave two 5-hydroxybicyclo[2.2.2]octan-2-ones and partial esterification with butyryl chloride gave two monobutyrates. The other two isomers each gave a single, different 5-hydroxybicyclo[2.2.2]octan-2-one on oxidation, and each isomer also gave a single, different monobutyrate. The stereoisomers **2a** and **3a** were distinguished from the ^{13}C NMR spectra,[3] and by the ^1H NMR spectra of their respective monobutyrates, taken in the presence of $Eu(DPM)_3$.

The ^1H NMR spectrum of **2b** in $CDCl_3$ with 0.1 equiv of $Eu(DPM)_3$ showed the C-7, C-8 bridge protons appearing in the same region as the β-CH_2 protons of the *n*-butyryl group, these protons thus experiencing only a small downfield shift. By contrast, under the same conditions the C-7, C-8 bridge protons in **3b** were all shifted further downfield, the protons syn to the OH group being more deshielded than those syn to the ester group.[4] The chemical shift of the other protons in the spectra of **2b** and **3b** were also in accord with the stereochemical assignment.

Reduction of **1** with lithium aluminum hydride gave essentially the same composition of diols, but reduction with lithium tri-*tert*-butoxyaluminum hydride gave a mixture comprised almost exclusively of the isomers **3a** and **4a.**

In contrast, reduction of the keto acid **6a** with sodium borohydride gave only one isomer, the known syn alcohol **7a.**[5] However, when the 2-methyl derivative **6b** was reduced under the same conditions, besides the predominant syn isomer **7b,** some of the anti isomer **8b** was also obtained. The assigned stereochemistry of these isomers was confirmed by the conversion of **7a** and **7b** into the respective lactones **9a** and **9b.**





The lack of stereoselective control in the reduction of **1** suggests that there is little preference for the approach of the borohydride to the first ketone group.[6,7] The smaller amount of **2a** compared to **4a** may indicate that the formation of the OH syn to the second ketone group assists in directing the borohydride from that side of the molecule.[8] The syn carboxylic acid group of **6a** presumably shields the ketone function from attack on that side, allowing exclusive formation of **7a.** We suspect that the lower stereoselectivity found in the reduction of **6b** is caused by increased steric shielding from the C-7,8 bridge on the ketone owing to the interaction with the C-2 methyl group, which forces these carbons closer to the C-5,6 bridge.

Experimental Section

^1H NMR spectra ($CDCl_3$) were recorded on either a Varian T-60 or HA-100 spectrometer using Me_4Si as internal standard and are reported in δ units. ^{13}C NMR spectra ($CDCl_3$) were recorded on a