sodium carbonate solution for 4 hr, extracted with ether, and dried (Na_2SO_4), and ether was separated by glc: mass spectrum *m/e* (rel intensity) 43 (85), 85 (100), 110 (25), 129 (M^+, 9); relative abundance of molecular ions,[20] 128 (45.5), 129 (100), 130 (17.1), 131 (3.0).

5-Ethylheptane-1,3-diol (45).—Methyl 5-ethyl-3-oxoheptanoate was synthesized by the method of Weiler[21] from methyl acetoacetate (3.48 g, 30 mmol) and 3-bromopentane (6.6 g, 33 mmol), bp 116–118° (18 mm), yield 1.4 g, (40%) from methyl acetoacetate. Reduction of this β-keto ester by the method of Cope and Wood[22] gave **45** in 83% yield: bp 126–130° (8 mm); ir 3320, 2925, 1460, 1380, 1050 cm^{-1}; mass spectrum of trimethylsilyl derivative *m/e* (rel intensity) 304 (M^+, 0.07), 289 (2), 261 (4), 219 (53), 187 (46), 103 (100), 73 (79).

Anal. Calcd for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.57; H, 12.66.

(20) Relative abundances of molecular ions of undeuterated **48** were as follows: *m/e* (rel intensity) 128 (100), 129 (9.3), 130 (0.6).

(21) L. Weiler, *J. Amer. Chem. Soc.*, **92**, 6702 (1970).

(22) A. C. Cope and G. W. Wood, *ibid.*, **79**, 3885 (1957).

5-Ethylheptane-1,4-diol (43).—Hydroboration of **42** at 0° under nitrogen and usual work-up gave **43** (purity 99% by glc): bp 120–125° (6 mm); mass spectrum of trimethylsilyl derivative *m/e* (rel intensity) 304 (M^+, 0.05), 289 (1), 247 (2), 233 (19), 143 (100), 73 (57).

Anal. Calcd for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.48; H, 12.84.

Registry No.—**1**, 112-43-6; **2**, 32970-48-2; **3**, 32970-49-3; **12**, 32970-50-6; **13**, 32970-51-7; **14**, 32970-52-8; **15**, 7289-47-6; **16**, 32970-54-0; **21**, 32970-55-1; **22**, 32970-56-2; **23**, 32970-57-3; **24**, 32970-58-4; **42**, 998-67-4; **43**, 32970-60-8; **45**, 33021-05-5; **48**, 6022-26-0.

Acknowledgment.—The authors are indebted to Mr. H. Kusakabe for mass spectra and Mrs. K. Huzimoto for elemental analyses.

Conformational Aspects of the Directive Effect of the Homoallylic Hydroxyl Group in the Simmons–Smith Reaction

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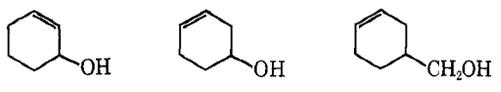
Received August 2, 1971

A series of substituted 3-cyclohexenols was prepared and subjected to the iodomethylzinc iodide methylenation reaction. Competitive kinetics establish that, in contrast to the allylic 2-cyclohexenols, the homoallylic 3-cyclohexenols react through the axial hydroxyl conformer. The compounds examined (k_{rel}) are 3-cyclohexenol (1.0), *cis*-6-methyl-3-cyclohexenol (5.2), 1-methyl-3-cyclohexenol (4.0), *trans*-6-methyl-3-cyclohexenol (2.6), *trans*-1,4,5,6,7,8-4a(8a*H*)-hexahydronapthol (1.6), and 4-methoxycyclohexene (0.18). All of these olefins exhibited stereospecific methylenation reactions.

Since its introduction in 1958, the Simmons–Smith methylenation reaction[2] has been widely used in organic synthesis. A particularly interesting aspect is the directive effect of a neighboring hydroxyl group in the substrate olefin.[3] In cyclopentenes and cyclohexenes, an allylic or homoallylic hydroxyl group leads to stereospecific cis introduction of the methylene group. Higher cyclic olefins can give trans product with high selectivity provided the hydroxyl group–organometallic complex affords more facile access to the trans face of the olefin.[3] In our earlier work[4] it was established that both allylic and homoallylic hydroxyl groups in cyclohexene cause very large rate enhancement. In fact, both types of alcohols react immeasurably faster than the parent unsubstituted olefin, although a significant factor also separates the rates of **1** and **2**. Interestingly,



1 $k_{rel} = 11$ **2** 1.0 **3** very slow

when the hydroxyl group is removed to the γ position, as in **3**, the rate becomes comparable to that of cyclohexene itself, and the reaction becomes effectively nonstereoselective.[4] By determining the relative rates of methyl-substituted 2-cyclohexenols, it was established that the cis directive effect of the allylic hydroxyl group is exerted by this group in the pseudoequatorial conformation. This result bears on the question of the structure of the Simmons–Smith reagent in ether solution; models indicate that a monomeric iodomethylzinc species, in which the metal is complexed to the pseudoequatorial hydroxyl oxygen, cannot attain the necessary geometry for reaction with the double bond. For this reason a dimeric structure for the reactive organometallic species was proposed.[4]

The rate difference between **1** and **2**, as well as the lack of any significant influence (stereochemical or kinetic) of the hydroxyl group in compound **3**, clearly indicates, that the directive effect of the hydroxyl group has very specific geometric requirements. It was therefore of interest to determine which conformer of the homoallylic cyclohexenol causes cis selectivity.

Ginsig and Cross,[5] in applying the Simmons–Smith reaction to estr-5(10)-ene-3,17-diol, found that both the 3α and 3β alcohols gave stereospecific methylenation (cis to the homoallylic 3-OH group in both cases), but the 3α isomer was quite sluggish in reaction and required forcing conditions. Levine and coworkers[6] have presented convincing evidence that the preferred half-chair conformation of ring A in estr-5(10)-ene is such that the 3α hydroxyl group would be equatorial, and conversely the 3β group would be axial. The methylenation results[5] therefore would support the

(1) Author to whom correspondence should be addressed.

(2) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **80**, 5323 (1958).

(3) A recent discussion of this phenomenon and references to earlier work are found in the work of C. D. Poulter, E. C. Friedrich, and S. Winstein, *ibid.*, **91**, 6892 (1969).

(4) J. H. Chan and B. Rickborn, *ibid.*, **90**, 6406 (1968).

(5) R. Ginsig and A. D. Cross, *ibid.*, **87**, 4629 (1965).

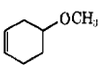
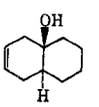
(6) S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Lett.*, 1517 (1963); S. G. Levine, D. M. Feigl, and N. H. Eudy, *ibid.*, 4615 (1967).

premise that the directive influence of the homoallylic hydroxyl group occurs preferentially *via* the axial conformer, in contrast to the allylic cyclohexenol[4] situation. However, long-range steric interactions in the steroidol systems could confuse this interpretation; we therefore decided to examine some simpler homoallylic cyclohexenols.

Results and Discussion

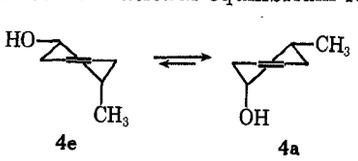
The competitive kinetic technique described earlier[4] was applied to the series of homoallylic alcohols shown in Table I. The unsubstituted 3-cyclohexenol **2** should

TABLE I
RELATIVE RATES OF METHYLENATION WITH IODOMETHYLZINC IODIDE

Olefin		k_{rel}
2		1.0
	(4)	5.2 ± 0.4
	(5)	4.0 ± 0.3
	(6)	2.6 ± 0.2
	(7)	0.18 ± 0.02
	(8)	1.6 ± 0.2

exist in two rapidly interconverting half-chair conformers. Although the conformational preference of the homoallylic hydroxyl group has not been determined, the experimental values for 4-methyl-[7] and the 4-halocyclohexenes[8] suggest that the hydroxyl group preference will be small. Compound **2** was therefore chosen as the reference material, with the expectation that alkyl-substituted analogs with stronger conformational preferences would exhibit either faster or slower rates of reaction with iodomethylzinc iodide.

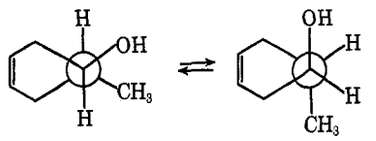
Compounds **4** and **5** both react faster than **2** (see Table I); this observation is compatible with the view that the homoallylic methyl group has a considerably stronger conformational preference than homoallylic hydroxyl, and that the directive effect of the hydroxyl group is exerted *via* its axial conformer. This is illustrated by the conformational equilibrium for **4** (eq 1).



4e 4a (1)

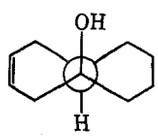
One would expect the equilibrium to favor **4a**, and, if **4a** is the conformer through which methylenation occurs, **4** should react more rapidly than **2**.

Conversely, the same reasoning indicates that compound **6** should undergo methylenation at a lower rate than **2**. This condition is not fulfilled, even though **6** is less reactive than **4** or **5**. One possible explanation for this apparent anomaly is that the gauche CH_3–OH interaction in **6e** causes **6a** to be favored (relative to the



6e 6a (2)

axial OH conformer of **2**). Alternatively, it may be that geminal or vicinal substitution by an alkyl group causes a distortion of the cyclohexene ring;[9] even a small change in geometry could lead to the rate differences observed for compounds **2**, **4**, **5**, and **6**. Ring distortion could in fact overshadow any conformational effects on rate and negate the conclusion regarding the preferred conformation for reaction. To circumvent this difficulty, compound **8** was prepared. As the Newman projection formula **8a** illustrates, this material



8a

is constrained conformationally by the trans-fused cyclohexane ring so that the hydroxyl group must remain axial. The rapid reaction of **8** shows conclusively that the directive influence of the homoallylic hydroxyl group is exerted through the axial conformation. The still faster rates of **4**, **5**, and **6**, even though the ground-state populations of their axial hydroxyl conformers cannot exceed that of **8**, may then be ascribed to the inherently lower flexibility of the latter compound.

We have earlier concluded[4] that the similarity in rates of Simmons–Smith methylenation of 2-cyclohexenol and its methyl ether (3-methoxycyclohexene) mitigated against a mechanism involving prior zinc salt formation with the alcohol. Since 3-cyclohexenol is a factor of ten less reactive than the 2-ol, the question of prior salt formation in the homoallylic system remains open. Using the same approach, it is found that 4-methoxycyclohexene (**7**) undergoes methylenation at a fivefold slower rate than **2**. Although this factor is somewhat greater than that observed with the allylic system, it is still too small to support any proposal of fundamentally different mechanisms for the alcohols and ethers. Simple complex formation between the oxygen atom and the zinc reagent is supported; this feature is common to the reactions of both the allylic and homoallylic systems.

In contrast to the situation with 2-cyclohexenol, the axial OH reactive conformation of the homoallylic alcohol does not preclude any particular state of aggregation for the Simmons–Smith reagent. Assuming first-order (in the organometallic) reaction with both alcohols, indirect support for a dimeric structure is provided.[4] The reason for the absence of any directive

(7) B. Rickborn and S. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).
(8) F. R. Jensen and C. H. Bushweller, *J. Amer. Chem. Soc.*, **91**, 5774 (1969).
(9) Distortion of this olefin by a single large group (4-*tert*-butyl) is well documented.[7,10]
(10) D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968).

effect, kinetic or stereochemical, for the γ-hydroxy group of **3** remains unclear.

Experimental Section

Kinetics.—Relative rate constants were determined as described previously,[4] using the following olefin pairs and vpc columns as indicated in footnote 11: **2** and **5**, column a[11] at 130°; **4** and **5**, column a at 130°; **2** and **6**, column b at 130°; **4** and **8**, column c at 185°; **2** and **7**, column c at 116°. At least three runs were made for each olefin pair, and vpc peak areas were corrected as described earlier.[12]

3-Cyclohexenol (2).—Reduction of benzene with lithium and ethanol in liquid ammonia[13] gave 1,4-cyclohexadiene; treatment of 125 g (1.56 mol) of this diene with 1 mol of peracetic acid[14] afforded, after distillation through a short Vigreux column, 100 g (67%) of 1,2-epoxy-4-cyclohexene, bp 62–63° (33 Torr). Reduction by $LiAlH_4$ gave 86 g (85%) of **2**, purified by distillation through a Teflon annular band column, bp 75.0–75.5° (15 Torr).[4]

A portion (7.0 g, 0.071 mol) of **2** was treated with sodium hydride and methyl iodide to furnish the ether **7**, 5.7 g (72%), bp 135–136°,[15] which was separated from traces of starting material contaminant by chromatography on alumina.

***cis*-6-Methyl-3-cyclohexenol (4) and 1-Methyl-3-cyclohexenol (5).**—Treatment of 276 g (3.0 mol) of toluene with 6 g-atoms of lithium wire and 9 mol of absolute ethanol in 2.5 l. of liquid ammonia gave 237 g (84%) of 1-methyl-1,4-cyclohexadiene,[16] bp 115–116°.

The diene, 237 g (2.52 mol), was treated with 1 equiv of peracetic acid.[14] Purification by distillation through a Teflon annular band column gave 209 g (75%) of 1-methyl-1,2-epoxy-4-cyclohexene, bp 153°. Integration of the nmr of this material showed a ratio of one epoxide proton to two vinyl protons.

The epoxide, 207 g (1.88 mol), was added slowly to an ice-cooled, stirred solution of 50 g (1.32 mol) of lithium aluminum hydride and 176 g (1.32 mol) of aluminum chloride in 2.1 l. of ether.[17] After the addition was complete the mixture was stirred for a few minutes and then hydrolyzed by sequential treatment with 50 ml of water, 50 ml of 15% sodium hydroxide solution, and 150 ml of water. The ether was decanted and the salt residue was washed several times with fresh solvent. The combined ether solutions were dried, evaporated, and distilled, bp 58–68° (6 Torr), to give 135 g (64%) of alcohol product. Vpc analysis (column a)[11] indicated a nearly equimolar mixture of the tertiary and secondary alcohol products.

Pure samples were readily obtained by redistillation through the Teflon annular band column.

1-Methyl-3-cyclohexenol (5): bp 70–71° (33 Torr); nmr ($CDCl_3$) δ 1.24 (s, 3), 1.39–1.82 (m, 2), 1.82–2.38 (m, 4), 2.40 (s, OH), 5.40–5.90 ppm (m, 2); ir (CCl_4) 3350, 3590 cm^{-1}. *Anal.*[18] Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.68; H, 10.74.

***cis*-6-Methyl-3-cyclohexenol (4):** bp 89–90° (33 Torr); nmr (CCl_4) δ 1.03 (d, 3, J = 7 Hz), 1.68–2.90 (m, 5), 3.75 (s, OH), 4.07–4.40 (m, 1), 6.09–6.48 (m, 2); ir 3475 cm^{-1}. *Anal.* Found: C, 74.88; H, 10.51.

trans-**6-Methyl-3-cyclohexenol (6).**—Various methods for preparing this material by the addition of methylorganometallic reagents to 1,2-epoxy-4-cyclohexene were explored, and the results have been presented earlier.[19] The following procedure is the method of choice.

A solution of lithium dimethylcuprate[20] was prepared by the slow addition of 50 ml of 0.84 *M* methyllithium in ether to a stirred slurry of 2.60 g (0.021 mol) of cuprous thiocyanate in ether, maintained at −15°. Slow addition of 1,2-epoxy-4-cyclohexene, 2.02 g (0.021 mol), in ether was done at the reduced temperature, after which the mixture was allowed to warm to 0° (2.5 hr). The mixture was then hydrolyzed by the addition of 5 ml of 10% sodium hydroxide solution. The combined ether phases from extraction were dried, evaporated, and distilled through a short Vigreux column, bp 46–48° (2.5 Torr), to give 1.59 g (68%) of **6**. Vpc analysis of this material indicated >98% purity (column a):[11] nmr (CCl_4) δ 1.05 (d, 3, J = 5.5 Hz), 1.45–2.85 (m, 5), 3.25–3.82 (m, 1), 3.90 (s, OH), 5.75 ppm (br s, 2); ir 3330 cm^{-1}. *Anal.* Found: C, 74.87; H, 11.00.

Further structural evidence was provided by careful Jones oxidation of a sample of **4** to give 6-methyl-3-cyclohexenone; this in turn was reduced with lithium aluminum hydride to give a mixture of **4** (34%) and **6** (64%).

trans-**Bicyclo[4.4.0]dec-3-en-1-ol (8).**—Tetralin was reduced by lithium and ethanol in liquid ammonia to give bicyclo[4.4.0]-deca-1(5),3-diene, bp 65–70° (3.5 Torr).[21] The Korach procedure[14] using 120 g (0.89 mol) of peracetic acid gave on distillation 125.4 g (94%) of the tetrasubstituted epoxide, 11-oxatricyclo[4.4.1.0]undec-3-ene, bp 45–50° (0.10 Torr).[22]

Reduction of this epoxide, 118.4 g (0.79 mol), with aluminum hydride (prepared from lithium aluminum hydride and aluminum chloride in a 3:1 molar ratio[17]) in ether afforded, after distillation through a Vigreux column, 112.7 g (94%) of alcohol product, bp 36–40° (0.05 Torr). This material was further purified by chromatography on alumina: nmr (CCl_4) δ 0.75–2.10 (m, 14) and 5.34–5.64 (m, 2); ir (thin film) 3470 cm^{-1}. *Anal.* Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.91; H, 10.50.

Cyclopropanes.—The Simmons–Smith procedure was used to prepare samples of the cyclopropane derivatives described in this work. All methylenation products appeared as single, symmetrical peaks under a variety of vpc conditions,[11] and are therefore presumed to be isomerically pure. By analogy to the reaction of 3-cyclohexenol itself, these products are believed to have the methylene bridge *cis* to the hydroxyl group.

All products exhibited the high-field multiplets characteristic of *gem*-cyclopropyl protons, and had satisfactory ir and nmr spectra.

trans-4-Methylbicyclo[4.1.0]heptan-*cis*-3-ol (from methylenation of **6**). *Anal.* Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.79; H, 10.93.

trans-3-Methylbicyclo[4.1.0]heptan-*cis*-3-ol (from **5**). *Anal.* Found: C, 76.32; H, 11.32.

cis-4-Methylbicyclo[4.1.0]heptan-*cis*-3-ol (from **4**). *Anal.* Found: C, 76.31; H, 11.31.

Tricyclo[5.4.0.$0^{3,5}$]undecan-1-ol (from **8**). *Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.53; H, 11.04.

Registry No.—**2**, 822-67-3; **4**, 33066-05-6; **5**, 33061-16-4; **6**, 33066-06-7; **7**, 15766-93-5; **8**, 33066-07-8; 1,2-epoxy-4-cyclohexene, 6253-27-6; 1-methyl-1,2-epoxy-4-cyclohexene, 31152-30-4; *trans*-4-methylbicyclo[4.1.0]heptan-*cis*-3-ol, 33066-08-9; *trans*-3-methylbicyclo[4.1.0]heptan-*cis*-3-ol, 33066-09-0; *cis*-4-methylbicyclo[4.1.0]heptan-*cis*-3-ol, 33066-10-3; tricyclo[5.4.0.$0^{3,5}$]undecan-1-ol, 33061-19-7.

Acknowledgment.—This work was supported in part by the National Science Foundation, GP 6043.

(11) (a) 6 m × 3.2 mm 10% Carbowax 20M; (b) 6 m × 3.2 mm 15% diisodecylphthalate; (c) 6.5 m × 3.2 mm 18% XF-1150; (d) 6.5 m × 6.4 mm 13% Carbowax 4M; (e) 1.6 m × 6.4 mm 20% TCEP; (f) 3 m × 6.4 mm 10% Carbowax 20M, with 2% K_2CO_3 added to the solid support; (g) 2 m × 6.4 mm 20% SF-96.

(12) B. Rickborn and J. H. Chan, *J. Org. Chem.*, **32**, 3576 (1967).

(13) A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959).

(14) M. Korach, D. R. Nielsen, and W. H. Rideout, *ibid.*, **82**, 4328 (1960).

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(16) R. A. Benkeser, M. L. Burrows, J. J. Hazdra, and E. M. Kaiser, *J. Org. Chem.*, **28**, 1094 (1963).

(17) These conditions were chosen to maximize the amount of tertiary cleavage; see D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *J. Amer. Chem. Soc.*, **91**, 2649 (1969).

(18) Analysis by C. F. Geiger, 312 E. Yale St., Ontario, Calif.

(19) J. Staroscik and B. Rickborn, *J. Amer. Chem. Soc.*, **93**, 3046 (1971).

(20) H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.*, **17**, 1630 (1952).

(21) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(22) W. Hückel and U. Wörffel, *Chem. Ber.*, **89**, 2098 (1956).