Notes

The Synthesis and Configuration of *cis*-2,6-Dimethyl-1,4-cyclohexanedione, *r*-2,*c*-6-Dimethyl-*c*-4-hydroxycyclohexanone, and Two Related Diols[1]

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Received February 11, 1972

In conformational studies of 4-hydroxycyclohexanones,[2] a key compound needed for comparison was *r*-2,*c*-6-dimethyl-*c*-4-hydroxycyclohexanone[3] (**1**), mp 66°. We wish to report the preparation and configuration of this hydroxy ketone (**1**) and some related compounds shown in Scheme I.

Catalytic hydrogenation of 2,6-dimethylhydroquinone (**2**) with Rh/Al_2O_3 catalyst gave a mixture from which two diols were isolated: diol A, mp 139–140°, and diol B, mp 118–119°. The total hydrogenation product mixture contained *ca.* 60% of diol A and *ca.* 30% of diol B (gas chromatographic analysis). The assignment of configuration to diols A and B is based upon a comparison of their nmr spectra with those predicted for each of the four possible meso (**3**–**6**) and two possible *dl* (**7** and **8**) 2,6-dimethyl-1,4-cyclohexanediols (Chart I and Table I).

The very narrow CHOH proton nmr band widths, $W = 5 \pm 1$ Hz, observed for diols A and B are sufficient evidence to eliminate structures **5**–**8**; only the equatorial C-1 protons of diols **3** and **4** would be expected to exhibit such narrow band widths (Chart I and Table I). Structures **3** and **4** may be differentiated by comparison of their C-4 proton band widths. Thus, diol A, with a C-4 proton band width of 31 ± 1 Hz, must be assigned the all-cis diol structure **3** (C-4 proton axial). Diol B, with a C-4 proton band width of 11 ± 1 Hz, must be assigned diol structure **4** (C-4 proton equatorial). In addition to the C-1 and C-4 proton band width data, the number of methyl doublets observed adds further evidence tending to rule out structures **7** and **8** as possibilities (Table I).

The ir spectra of diols A and B, 0.004 *M* in carbon tetrachloride solution, are consistent with the assigned structures. Free hydroxyl OH stretching peaks were observed at 3643 and 3624 cm^{-1} for diol A and at 3642 and 3631 cm^{-1} for diol B. The higher frequency peaks (3642, 3643 cm^{-1}) may be attributed to the OH stretch-

SCHEME I

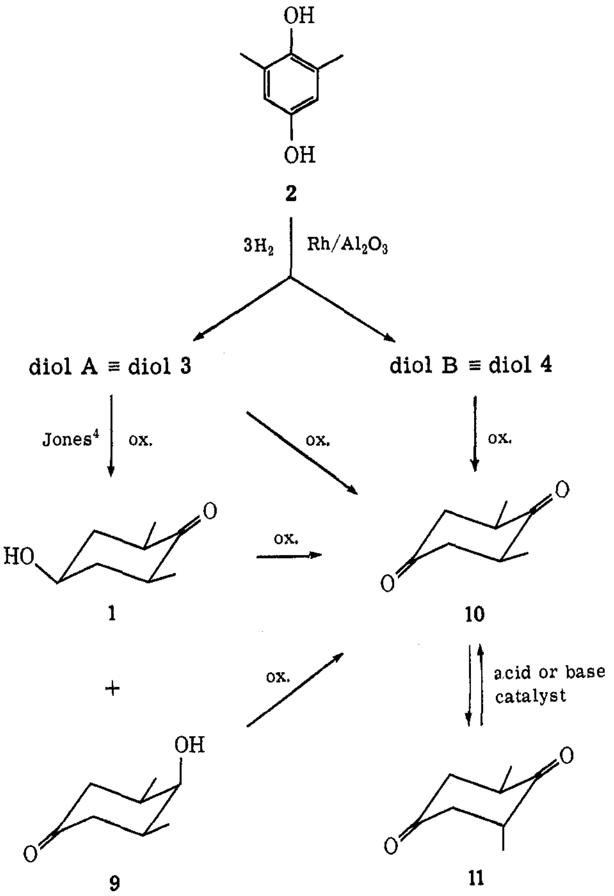
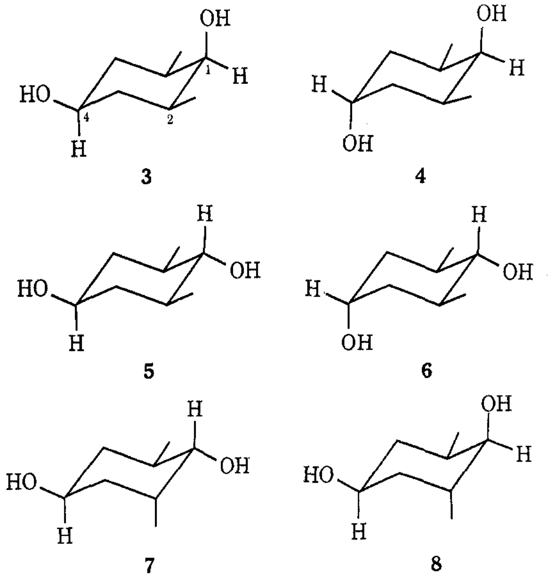


CHART I

THE 2,6-DIMETHYL-1,4-CYCLOHEXANEDIOLS



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[1] Taken in part from the Doctoral Dissertation of T. W. Giants, Tufts University, June 1971. This work was supported in part by Public Health Service Research Grant GM-08813 from the National Institutes of Health and in part by the National Science Foundation.

[2] R. D. Stolow, T. Groom, and M. Gerace, *J. Amer. Chem. Soc.*, **90**, 3290 (1968); T. Groom, Ph.D. Dissertation, Tufts University, 1969.

[3] Stereochemistry nomenclature rule E-3.3, *J. Org. Chem.*, **35**, 2849 (1970).

[4] J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Syn.*, **45**, 77 (1965); R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

TABLE I

COMPARISON OF THE OBSERVED NMR OF DIOLS A AND B WITH THE PREDICTED NMR OF DIOLS 3–8

Diol[a]	Number of CH_3 doublets	C-1 proton band width,[b] Hz	C-4 proton band width,[c] Hz
A	1	5 ± 1	31 ± 1
B	1	5 ± 1	11 ± 1
3	1	5 ± 1	30 ± 2
4	1	5 ± 1	12 ± 2
5	1	20 ± 2	30 ± 2
6	1	20 ± 2	12 ± 2
7	2	14 ± 2	30 ± 2
8	2	8 ± 2	26 ± 3

[a] The population of the conformer shown in Chart I is expected to be >99% for diols **3–6**, *ca.* 98% for diol **7**, and *ca.* 80% for diol **8**. [b] The sum of the two vicinal coupling constants involving the C-1 proton should equal the C-1 proton band width. The C-1 proton band widths predicted for diols **3–8** assumed $J_{1a,2a} = 10$, $J_{1a,2e} = 4$, $J_{1e,2a} = 2.5$, and $J_{1e,2e} = 3.5$ Hz.[d] [c] The sum of the four vicinal coupling constants involving the C-4 proton should equal the C-4 proton band width. The C-4 proton band widths predicted for diols **3–8** assume $J_{3a,4a} = 11$, $J_{3e,4a} = 4$, $J_{3a,4e} = 2.5$, and $J_{3e,4e} = 3.5$ Hz.[d] [d] These coupling constants are based in part upon values for analogous compounds determined by James L. Marini, Ph.D. Dissertation, Tufts University, 1969.[5,6]

ing vibration of a hindered axial C-1 hydroxyl group.[7] As found for 4-*tert*-butylcyclohexanol and related compounds,[8] one would expect the OH stretching frequency of the C-4 axial hydroxyl group to be greater than that of the C-4 equatorial hydroxyl group in diols A and B. Therefore, diol A (**3**) has an equatorial C-4 hydroxyl group (3624 cm^{-1}) while diol B (**4**) has an axial C-4 hydroxyl group (3631 cm^{-1}).

Chemical evidence also supports these assignments. Under the catalytic hydrogenation conditions used, the major product is expected to be the all-cis diol (**3**).[9] The result of the hydrogenation, formation of 60% of diol A, is consistent with the assignment of structure **3** to diol A. Furthermore, diols A and B yield the same dione upon Jones oxidation.[4] Therefore, diols A and B must have the same configuration at C-2 and C-6. Upon limited Jones oxidation,[4] diols A and B each give a different stereoisomeric 2,6-dimethyl-4-hydroxycyclohexanone. Therefore, diols A and B must differ in configuration at C-4 (as clearly shown by the C-4 proton band widths, Table I, and the ir frequencies given above). Taken together, the nmr, ir, and chemical results provide conclusive evidence supporting the assignment of structure **3** to diol A and structure **4** to diol B.

The Jones oxidation[4] of either diol **3** or **4** with excess reagent gave *cis*-2,6-dimethyl-1,4-cyclohexanedione (**10**). When the Jones oxidation of diol **3** was carried out with only enough reagent to convert half of the hydroxyl groups present to carbonyl groups, then in addition to the dione **10**, two hydroxy ketones (**1** and **9**) were also formed. The four-component mixture containing some unreacted diol **3**, dione **10**, and hydroxy ketones **1** and **9** was separated by preparative thin layer chromatography on silica gel. One component, mp 66–66.5°, isolated in 30% yield, was identified as hydroxy ketone **1**. A comparison of nmr spectra shows clearly that in the formation of hydroxy ketone **1**, the C-4 proton of diol **3** was retained while the C-1 proton was lost. The four-component mixture obtained by a similar limited Jones oxidation of diol **4** has not been separated successfully.

The equilibrium mixture of *cis* and *trans* diones (**10** $\rightleftarrows$ **11**), easily prepared by adding a trace of acid catalyst to a solution of cis dione **10**, had been obtained previously by hydrolysis of the lithium–ammonia–ethanol reduction product of the dimethyl ether of **2**.[10] The gas chromatographic peak height ratio for **10**:**11** in the equilibrium mixture was 57:43.[11]

Experimental Section

Routine nmr spectra were recorded by use of a Varian A-60A spectrometer.[12] Nmr band widths were obtained by use of a Varian HA-100 spectrometer locked on internal tetramethylsilane.

Infrared spectra (OH bands) were recorded as previously reported,[13] by use of 0.004 *M* solutions of the diols in dried Spectranalyzed carbon tetrachloride in 1.00-cm cells at *ca.* 25°. Routine infrared spectra were recorded by use of a Perkin-Elmer 237B spectrophotometer.[12]

Gas chromatography was carried out at 114° by use of an F and M 5750 flame ionization gas chromatograph with a 90 cm, 0.188 in. o.d. copper column packed with 4% Versamid 900 (General Mills) on 100–120 mesh Gas Chrom P. The column was conditioned before use by heating in an oven at 200° for 2 hr without gas flow and then at 180° for 24 hr with 15 ml/min dried nitrogen gas flow through the column.[11]

Melting points were determined in open Pyrex capillary tubes by use of an oil bath apparatus and are corrected. Microanalyses were performed by Dr. S. M. Nagy and by Spang Microanalytical Laboratory.

Hydrogenation of 2,6-Dimethylhydroquinone (2).—To a solution of 10.9 g (76.0 mmol) of 2,6-dimethylhydroquinone (**2**), mp 152.5–153°, dissolved in 80 ml of absolute ethanol (reagent quality) in a 500-ml Parr bottle were added 1 ml of acetic acid and 3.0 g of 5% rhodium on alumina catalyst (Engelhard Ind.). Hydrogenation at 30° and 3 atm initial pressure of hydrogen was complete in 29 hr. Removal of catalyst and solvent gave 11 g (100%) of a solid product mixture. Gas chromatographic analysis of the mixture showed the presence of 60% of diol **3**, 30% of diol **4**, and very small amounts of at least two other components (presumably isomeric diols).[14]

***cis,cis*-2,6-Dimethyl-*cis*-1,4-cyclohexanediol (*c*-2,*c*-6-Dimethyl-*r*-1,*c*-4-cyclohexanediol[3]) (3).**—Recrystallization of the above product mixture four times from benzene gave 5 g (45%) of white crystals, mp 137.5–139°. Gas chromatography gave a single peak. Further recrystallization gave diol **3**: mp 139–140°; ir (Nujol) 1377, 1118, 1030, 980, 937, and 860 cm^{-1}; nmr [$(CD_3)_2SO$ + 2% DCl in D_2O] δ 0.88 (d, *J* = 5.5 Hz, 6, CH_3), 1.0–1.6 (m, 6, CH_2 and CH_3CH), 2.52 (quintet, CD_3SOCD_2H), 3.23 (unresolved m, 1, CHCHOH), 3.4 (m, 1, CH_2CHOH), and 3.8 (s, 2, OH). **3** is entered in Table I as diol A.

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.59; H, 11.29.

***cis,cis*-2,6-Dimethyl-*trans*-1,4-cyclohexanediol (*c*-2,*c*-6-Dimethyl-*r*-1-*t*-4-cyclohexanediol[3]) (4).**—A sample (0.65 g) of the

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(5) R. D. Stolow and J. L. Marini, *Tetrahedron Lett.*, 1449 (1971).

(6) H. Booth in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. 5, J. W. Emsley, J. Feeney and L. H. Sutcliffe, Ed., Pergamon Press, Oxford, 1969, p 149.

(7) For a comparison of our result with values for other hindered alcohols, see R. E. Lyle and D. H. McMahon, *Tetrahedron Lett.*, 4885 (1967).

(8) H. S. Aaron, C. P. Ferguson, and C. P. Rader, *J. Amer. Chem. Soc.*, **89**, 1431 (1967), and references cited therein.

(9) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N. Y., 1967.

(10) M. M. Bonaventura, Ph.D. Dissertation, Tufts University, 1965; H.-J. Teuber, D. Cornelius, and U. Wölcke, *Justus Liebigs Ann. Chem.*, **696**, 116 (1966).

(11) A. E. Clements, M.S. Thesis, Tufts University, 1965.

(12) Nmr and infrared spectra of diols **3** and **4** have been reproduced in the Doctoral Dissertation of T. W. Giants, Tufts University, 1971.

(13) R. D. Stolow, P. M. McDonagh, and M. M. Bonaventura, *J. Amer. Chem. Soc.*, **86**, 2165 (1964).

(14) P. F. Wiley and O. Weaver, *J. Org. Chem.*, **25**, 1664 (1960), reported the catalytic hydrogenation of 2,6-dimethyl-*p*-benzoquinone with Raney nickel at 180°, conditions which gave considerable hydrogenolysis and only 14% of liquid diol product mixture.

residue obtained by evaporation of the benzene filtrates above was chromatographed on a column of neutral alumina (Fluka, type 507C, 47.5 g, shaken with 1.5 ml of water for 1 hr). After elutions with hexane and benzene, elution with anhydrous ether gave 0.4 g of solid. Recrystallization from benzene gave 0.25 g of white crystals, mp 118–119°, which showed a single peak upon gas chromatography: ir (Nujol) 1375, 1181, 1145, 1008, 963, 938, and 808 cm^{-1}; nmr [$(CD_3)_2SO$ + 2% DCl in D_2O] δ 0.85 (d, J = 6.2 Hz, 6, CH_3), 1.2–2.2 (m, 6, CH_2 and $CH_3C\mathbf{H}$), 2.57 (quintet, CD_3SOCD_2H), 3.37 (unresolved m, 1, $CHC\mathbf{H}OH$), 3.88 (quintet, 1, $CH_2C\mathbf{H}OH$), and 4.1 (s, 2, OH). **4** is entered in Table I as diol B.

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found, C, 66.97; H, 11.11.

Continued elution with 19:1 ether–methanol gave a second fraction, 0.25 g, mp 139–141°, identified as diol **3**.

***r*-2,*c*-6-Dimethyl-*c*-4-hydroxycyclohexanone**[3] (*1*).—To a solution of 0.40 g (3.4 mmol) of diol **3** in 15 ml of acetone (reagent grade, purified by distillation from $KMnO_4$), stirred vigorously in an ice–salt–water bath at −5°, was added dropwise 0.89 ml (1 equiv) of 2.5 *M* chromic acid solution[4] during 15 min. After stirring for an additional 15 min at −5°, a chilled solution of 1.3 g of $NaHSO_3$ in 40 ml of water was added and the mixture was extracted immediately with 6 × 100 ml of chilled ether. The ether layer was washed with 2 × 15 ml of cold 10% $NaHCO_3$ and then with 15 × 4 ml of cold water. The final washings were neutral. The ether layer was dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure gave a viscous oil which showed four peaks upon gas chromatography. One peak gave the same retention time as the starting material, diol **3**. The three expected products are hydroxy ketones **1** and **9** and dione **10**. Thin layer chromatography also showed four components.

The product was applied to three preparative thin layer chromatography plates, 20 × 20 cm, coated with a 2-mm layer of silica gel (E. Merck, PF_{254}). Double development with 1:1 anhydrous ether–benzene gave separation of the components. Each band was extracted with 10 × 20 ml of anhydrous ether. Filtration, removal of solvent under reduced pressure, and recrystallization from hexane gave from one band 0.12 g (30%) of fluffy white crystals, mp 66–66.5°, assigned structure **1**: nmr[2] (CD_3OD) δ 0.97 (d, J = 5.5 Hz, 6, CH_3), 1–3 (m, 6, $CH_3C\mathbf{H}$-$C\mathbf{H}_2$), 4.2 (nonet, 1, $C\mathbf{H}OH$, band width 30.2 ± 0.2 Hz), and 4.7 (s, 1, OH); nmr[2] (benzene) 4.0 (nonet, 1, $C\mathbf{H}OH$, band width 29.5 ± 0.2 Hz).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.72; H, 10.16.

Similarly, a second band yielded an oily residue, which after recrystallization from hexane gave 0.08 g (20%) of white, fluffy crystals, mp 53–54°, not fully characterized, but probably *r*-3,*c*-5-dimethyl-*c*-4-hydroxycyclohexanone (**9**).[14]

***cis*-2,6-Dimethyl-1,4-cyclohexanedione (10). A. Jones Oxidation of Diol 3.**—To 2.50 g (0.0173 mol) of diol **3** in 88 ml of acetone (distilled from $KMnO_4$) at 0° was added dropwise with vigorous stirring 18.7 ml (100% excess) of 2.48 *M* chromium oxide solution[4] during 15 min. The temperature was maintained at 0–5° during the addition and for 15 min of further stirring following the addition. Then 3.62 g of $NaHSO_3$ in 88 ml of water at 0° was added. The resulting green solution was immediately extracted with 3 × 290 ml of ether. Each ether extract was washed successively with 110 ml of 10% NH_4Cl, 110 ml of 10% $NaHCO_3$, and 66 ml of water. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure to give 2.2 g (90%) of a white solid, mp 85–87°. Two recrystallizations from hexane gave 1.3 g of cis dione **10**, mp 87.5–88°, containing *ca.* 1% of the trans epimer, detected by gas chromatography.[11]

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.73; H, 8.64.

B. Jones Oxidation of Diol 4.—As above, but on a smaller scale, 0.28 g (0.0019 mol) of diol **4** gave 0.24 g (89%) of white solid, mp 86–87.5°. Recrystallization from hexane gave 0.19 g of cis dione **10**, mp 87.5–88.5°. Reaction of **10** with excess 1,2-ethanedithiol and boron trifluoride–ether gave a product, mp 95–96° (from methanol).

Registry No.—**1**, 34958-40-2; **3**, 34958-41-3; **4**, 34958-42-4; **10**, 34958-43-5.

Bicyclo[3.2.1]oct-6-en-2-one. A Convenient Synthesis of Bridged Polycyclic, Homoconjugated Ketones[1,2]

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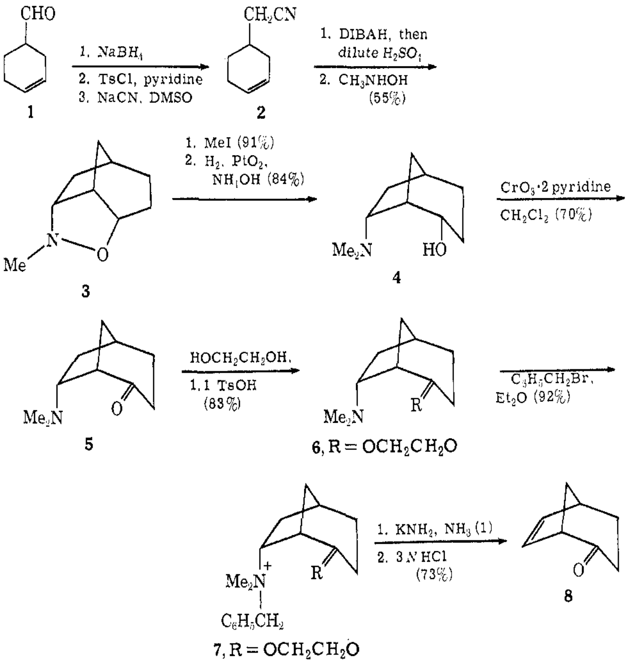
Received January 6, 1972

As part of a continuing program of exploration of the mechanistic nuances and the synthetic scope of intramolecular 1,3-dipolar cycloadditions of nitrones, we have prepared a variety of polycyclic isoxazolidines.[3] It is the purpose of this report to describe a simple and efficient degradation scheme which will allow conversion of certain of these products to homoconjugated (γ,δ-unsaturated) ketones. These latter are of both theoretical and preparative import.

The key compound of the present example is the tricyclic isoxazolidine **3**, which was prepared by the reaction of 3-cyclohexen-1-acetaldehyde with *N*-methylhydroxylamine. The aldehyde was obtained by diisobutylaluminum hydride reduction of 3-cyclohexen-1-acetonitrile (**2**). Quaternization of **3** with methyl iodide followed by hydrogenolysis gave the amino alcohol **4**, which was in turn oxidized to the *N*,*N*-dimethylamino ketone **5**.[4] The ethylene ketal **6** was then prepared, and it was benzylated to afford **7**.[5] Reaction with potassium amide in liquid ammonia and



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(1) This work was supported by the National Science Foundation under Grant No. GP 14114.

(2) For the previous paper in this series, see N. A. LeBel and E. G. Banucci, *J. Org. Chem.*, **36**, 2440 (1971).

(3) N. A. LeBel, *Trans. N. Y. Acad. Sci.*, **27**, 858 (1965); N. A. LeBel, G. H. J. Slusarczuk, and L. A. Spurlock, *J. Amer. Chem. Soc.*, **84**, 4360 (1962).

(4) The Collins oxidation procedure, ref 9, has proven superior in our hands; however, Jones, Kiliani, and Sarett oxidations were successful in varying degrees.

(5) Benzylation proved superior to methylation because the subsequent elimination reaction generated improved yields of product **8**.