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Hydrogenation and Conformational Analysis of (1*R*,2*R*,6*S*)-3-Methyl-6-(1-methylethenyl)cyclohex-3-ene-1,2-diol

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Abstract—Hydrogenation of (1*R*,2*R*,6*S*)-3-methyl-6-(1-methylethenyl)cyclohex-3-ene-1,2-diol was studied. Nickel chloride–sodium tetrahydridoborate system turned out to selectively reduce the double bond in the isopropenyl group. The results of conformational analysis of (1*R*,2*R*,6*S*)-3-methyl-6-(1-methylethenyl)cyclohex-3-ene-1,2-diol and its partly and completely hydrogenated derivatives were in a good agreement with the NMR data.

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We recently found [1] that (1*R*,2*R*,6*S*)-3-methyl-6-(1-methylethenyl)cyclohex-3-ene-1,2-diol (**I**) formed by isomerization of (–)-*cis*-verbenol epoxide (**II**) over montmorillonite clays (Scheme 1) [2] exhibits a strong anticonvulsant activity. Therefore, synthesis of various derivatives of compound **I** seems to be promising. The goal of the present work was to develop a procedure for selective hydrogenation of diene **I** to enediol **III**.

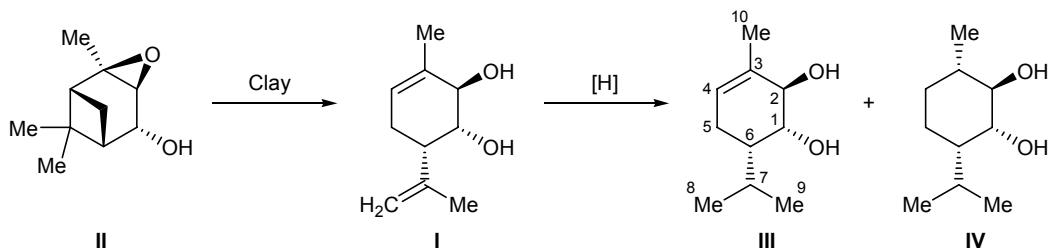
The reduction of compound **I** with hydrogen over Raney nickel under pressure was characterized by poor selectivity. Depending on the temperature and reaction time, mixtures of unreacted compound **I** with partly hydrogenated product **III** or of partly and completely hydrogenated products **III** and **IV** were obtained, and it was difficult to separate them. For example, the reduction at 60°C (12 h, 100 atm) gave 63% of a mixture of **III** and **IV** at a ratio of 1 : 0.4.

We have found that an efficient system for selective hydrogenation of the exocyclic double bond in **I** may be nickel(II) hydridoborate generated *in situ* from $NiCl_2$ and $NaBH_4$. This system was successfully used previously for reductive amination of aldehydes and ketones [3], reduction of azides to amines [4] and aromatic nitro compounds to anilines [5], and catalytic hydrogenation of double bonds with molecular hydrogen [6].

Diol **I** was reduced on heating in boiling methanol over a period of 5 h, and the yield of compound **III** isolated and purified by column chromatography was 66%. Thus nickel borohydride turned out to be appropriate for the selective reduction of the exocyclic double bond in compound **I**.

The structure of compounds **III** and **IV** was determined on the basis of the ^1H and ^{13}C NMR data. Un-

Scheme 1.



II **I** **III** **IV**

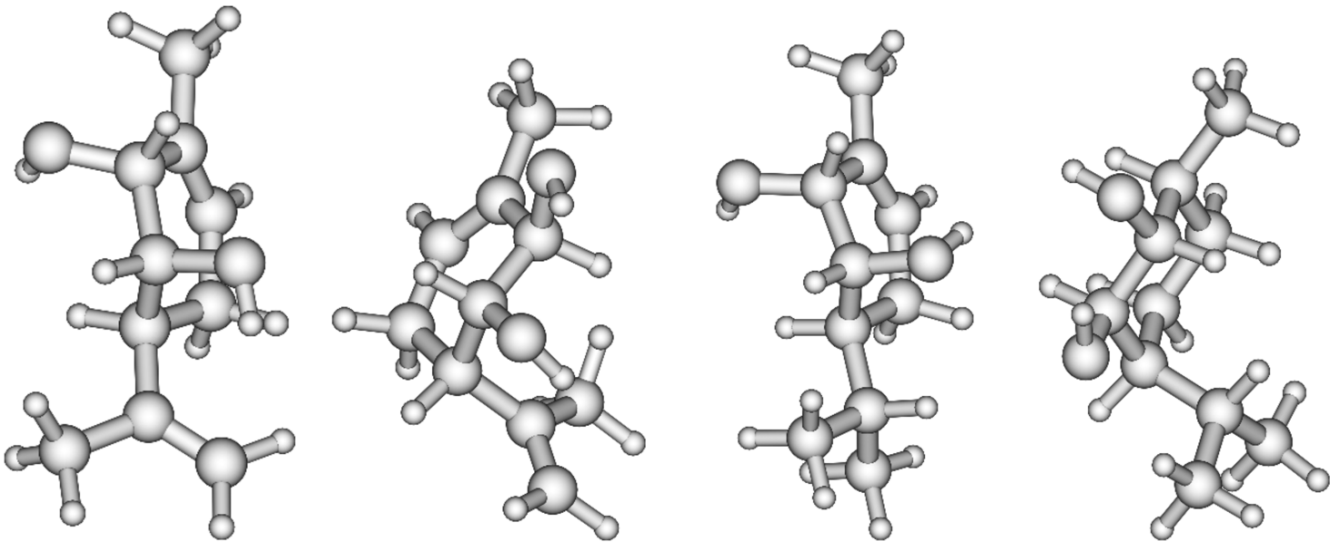
like compounds **I** and **III**, the 1-H and 2-H protons in diol **IV** displayed a quite different vicinal coupling constant ($J_{1,2}$ = 8.5 Hz); in addition, coupling between the 2-H and 3-H protons was observed ($J_{2,3}$ = 8.5 Hz). These data indicated axial orientation of the above three protons. In keeping with the $J_{1,6}$ value equal to 4.5 Hz, the 6-H proton occupies equatorial position, and hence the bulky isopropyl group is axial. In order to rationalize the observed pattern, detailed conformational analysis of compounds **I**, **III**, and **IV** was performed.

Conformational analysis is very important from the viewpoint of medicinal chemistry, for biological activity of structurally nonrigid organic molecules is largely determined by their conformation [7]. Another important field of application of conformational analysis is prediction of steric structure and related spectral parameters, in particular spin–spin coupling constants in NMR spectra. Most generally, conformational analysis is performed with a view to find most stable conformations, though in some cases less favorable structures should also be taken into account. Biologically active conformation does not necessarily correspond to the global minimum on the potential energy surface (PES), and it can be characterized by a higher energy ($\Delta E \leq$ 40 kJ/mol) [8]. In addition, contributions of conformers having similar energy (which are capable of undergoing fast interconversion) must be considered while analyzing the NMR spectra.

It should be noted that even search for most stable conformation is not a trivial problem. Such widely used computer programs as ChemDraw-Chem3D, ChemSketch, and MarvinSketch make it possible to quickly draw a two-dimensional structure and automatically convert it into three-dimensional. However, this is frequently insufficient, for the resulting conformation is not necessarily the most stable. As applied to compound **I**, the above three programs (after additional DFT optimization) gave three different structures, but none of them corresponded to the global minimum on the potential energy surface; only one program (ChemSketch) correctly predicted equatorial orientation of the isopropenyl group.

Conformational analysis of compounds **I**, **III**, and **IV** was performed in three steps. Initial sets of conformations were obtained by the molecular mechanics method using several conformer generators. In the second step, the conformer structures were optimized in terms of semiempirical quantum-chemical methods. Finally, the remaining structures were optimized at the DFT level. After each step, doubles (i.e., structures with equal or very similar geometric parameters) were removed, so that the number of structures decreased (especially strongly in the second step). For example, conformer generators (Marvin, Vconf, and Tinker) proposed in total 274 structures for diol **I**, 172 of which were unique. After optimization in the second step (RM1 MOPAC2009), only 54 structures remained, and DFT optimization (PBE/L1, PRIRODA) left 28 structures. Ultimately, we obtained 35 and 38 conformers for diols **III** and **IV**, respectively.

The most populated energy levels of initial compound **I** corresponded to conformers with equatorial



I-*eq* **I**-*ax* **III** **IV**

Most stable conformations of compounds **I**, **III**, and **IV**.

isopropenyl group. The overall fraction of such conformers was 72%; it was estimated on the basis of the calculated energies according to the Boltzmann distribution at 25°C. In this case, the contribution of conformers with axial orientation of the isopropenyl group was also significant (28%). Figure shows the most stable conformations with equatorial and axial isopropenyl groups. According to the calculations, hydrogenated derivatives of diol **I** are conformationally homogeneous. The isopropyl group in almost all conformers of compound **III** (overall fraction 97%) occupies equatorial position. In contrast, conformers of completely hydrogenated compound **IV** with axial orientation of the isopropyl group turned out to be much more stable (overall fraction ~100%). In all cases, the results of conformational analysis were consistent with the structures of compounds **I**, **II**, and **IV** determined on the basis of the NMR data.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500.13 and 125.76 MHz, respectively, from solutions in $CDCl_3$–CCl_4 (~1:1 by volume); the chemical shifts were determined relative to the residual proton and carbon signals of the solvent ($CHCl_3$, δ 7.24 ppm; $CDCl_3$, δ_C 76.90 ppm). Signals were assigned with the aid of ^{1}H–^{1}H double resonance techniques and two-dimensional heteronuclear (^{13}C–^{1}H) correlation technique (C–H COSY, direct C–H coupling constants, $^1J_{CH}$ = 135 Hz). The high-resolution mass spectra were obtained on a DFS Thermo Scientific spectrometer (total ion scanning in the a.m.u. range from 0 to 500; electron impact, 70 eV; direct sample admission into the ion source). The specific rotations $[\alpha]_D$ were determined on a polAAr 3005 polarimeter.

(1*R*,2*R*,6*S*)-3-Methyl-6-(1-methylethenyl)cyclohex-3-ene-1,2-diol (**I**) was synthesized according to the procedure described in [2]; $[\alpha]_D^{31}$ = –49.1° (*c* = 2.6, $CHCl_3$).

Hydrogenation of (1*R*,2*R*,6*S*)-3-methyl-6-(1-methylethenyl)cyclohex-3-ene-1,2-diol (I) with nickel borohydride. Triethylamine, 1.0 ml (7.22 mmol), was added to a solution of 2.18 g (9.16 mmol) of $NiCl_2 \cdot 6H_2O$ in 10 ml of methanol, a solution of 0.201 g (1.20 mmol) of compound **I** in 7 ml of methanol was added, 0.622 g (16.36 mmol) of $NaBH_4$ was then added in portions over a period of 2 min, and the mixture was heated for 5 h under reflux. The mixture was diluted with 20 ml of water, methanol was distilled off, 60 ml of 25% aqueous ammonia and 50 ml of ethyl acetate were added to the residue, and the mixture was filtered through a layer of silica gel. The organic phase was separated, the aqueous phase was extracted with ethyl acetate (3 × 20 ml), and the extracts were combined with the organic phase, washed with 5% hydrochloric acid (3 × 20 ml) and a saturated solution of NaCl–$NaHCO_3$ (2 × 20 ml), dried over Na_2SO_4, and evaporated. The residue, 0.154 g, was separated by column chromatography on silica gel (60–200 μm, Macherey Nagel) using hexane–ethyl acetate (gradient elution, 10 to 50% of EtOAc) as eluent to isolate 0.135 g (0.79 mmol, 66%) of diol **III**.

(1*R*,2*R*,6*S*)-6-Isopropyl-3-methylcyclohex-3-ene-1,2-diol (III). $[\alpha]_D^{22}$ = –89.4° (*c* = 2.67, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.91 d and 0.96 d (C^8H_3, C^9H_3, $J_{8,7} = J_{9,7}$ = 6.8 Hz), 1.30 m (6-H_{ax}), 1.62 d.q.q (7-H, $J_{7,6\text{-}ax}$ = 10.0, $J_{7,8} = J_{7,9}$ = 6.8 Hz), 1.76 d.d.d ($C^{10}H_3$, $J_{10,5\text{-}ax}$ = 2.2, $J_{10,4} = J_{10,5\text{-}eq}$ = 1.5 Hz), 1.78 m (5-H_{ax}), 2.08 d.d.d.q (5-H_{eq}, ^2J = 17.5, $J_{5\text{-}eq,4} = J_{5\text{-}eq,6a}$ = 5.0, $J_{5\text{-}eq,10}$ = 1.5 Hz), 3.71 d (2-H_{eq}, $J_{2\text{-}eq,1\text{-}eq}$ 3.0 Hz), 3.90 br.d.d (1-H_{eq}, $J_{1\text{-}eq,2\text{-}eq}$ = 3.0, $J_{1\text{-}eq,6\text{-}ax}$ = 1.5 Hz), 5.57 d.m (4-H, $J_{4,5\text{-}eq}$ = 5.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 70.76 d (C^1), 72.61 d (C^2), 131.58 s (C^3), 125.77 d (C^4), 25.32 t (C^5), 38.88 d (C^6), 28.59 d (C^7), 20.72 q and 20.80 q (C^8, C^9), 21.05 q (C^{10}). Found: *m*/*z* 170.1302 $[M]^+$. $C_{10}H_{18}O_2$. Calculated: *M* 170.1301.

Hydrogenation of (1*R*,2*R*,6*S*)-3-methyl-6-(1-methylethenyl)cyclohex-3-ene-1,2-diol (I) with hydrogen over Raney nickel. Raney nickel was prepared according to the procedure described in [9] from Al–Ni alloy containing 30–50% of Ni. A 400-ml high-pressure reactor was charged with a solution of 0.670 g (3.99 mmol) of compound **I** in 50 ml of ethanol, and hydrogen was supplied to a pressure of 100 atm at 60°C over a period of 12 h. When the reaction was complete, the catalyst was filtered off, the filtrate was passed through a column charged with silica gel, and the solvent was distilled off to isolate 0.436 g (63%) of a mixture of compounds **III** and **IV** (1:0.4).

(1*R*,2*R*,3*S*,6*S*)-3-Isopropyl-6-methylcyclohexane-1,2-diol (IV). ^{1}H NMR spectrum, δ, ppm: 0.86 d and 1.04 d (C^8H_3, C^9H_3, $J_{8,7} = J_{9,7}$ = 6.8 Hz), 1.00 d ($C^{10}H_3$, $J_{10,3}$ = 6.5 Hz), 1.40 m (3-H_{ax}), 1.47 m (4-H_{eq}), [1.31] and [1.69] (5-H), [1.56] (6-H), [1.75] (7-H), 3.27 d.d (2-H_{ax}, $J_{2\text{-}ax,1\text{-}ax}$ = 8.5, $J_{2\text{-}ax,3\text{-}ax}$ 8.5 Hz), 3.57 d.d (1-H_{ax}, $J_{1\text{-}ax,2\text{-}ax}$ = 8.5, $J_{1\text{-}ax,6\text{-}eq}$ 4.5 Hz). The values given in brackets (positions of centers of multiplets) were taken from two-dimensional ^{13}C–^{1}H correlation spectra

(direct ^{13}C–^{1}H coupling), for the corresponding signals were not observed in the routine spectrum due to overlap by signals of the major component. ^{13}C NMR spectrum, δ_C, ppm: 77.71 d (C^1), 76.14 d (C^2), 37.71 d (C^3), 28.59 t (C^4), 25.42 t (C^5), 45.00 d (C^6), 26.28 d (C^7), 23.40 q and 21.97 q (C^8, C^9), 18.29 q (C^{10}). Found: *m*/*z* 172.1456 $[M]^+$. $C_{10}H_{20}O_2$. Calculated: *M* 172.1458.

Conformational analysis of compounds I, III, and IV. The initial set of conformers was generated by the molecular mechanics method using ChemAxon Marvin (*conformers* plugin) [10], VeraChem Vconf [11] (Dreiding force field), and Scan program incorporated into Tinker software [12] (MM2 force field). The structures were optimized first by the RM1 method [13] using MOPAC2009 [14] and then by DFT (PBE functional [15], L1 basis set (Λ01 [16], an analog of cc-pVDZ) using Priroda software [17]). Doubles were removed after each optimization step with the aid of *conformers* program [*http://limor1.nioch.nsc.ru/quant/program/conformers/*]. Structure visualizations and files containing Descartes coordinates of all conformers are available at *http://limor1.nioch.nsc.ru/quant/conformers/diols/*.

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