

## CATALYTIC OSMYLATION OF CIS AND TRANS 2-CYCLOHEXENE-CYCLOHEXANOL

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**ABSTRACT :** *Catalytic osmylation of cis and trans 2- cyclohexene- cyclohexanol (1a) and (1b) are carried out in the presence of N- methyl morpholine-N- oxide. Under the same conditions, only the cis isomer reacted, leading to triol (3). The steric hindrance of the equatorial OH group probably prevents the trans isomer from entering into such reaction. Triol (3) was also obtained from the reduction of the diol- ketone (4).*

**KEY WORDS :** *Osmylation, N- methylmorpholine-N-oxide, Cis and trans-2- cyclohexene - cyclohexanol, Hydroxylation.*

### INTRODUCTION

The reaction of olefinic compounds with osmium tetroxide is one of the most reliable methods for hydroxylation of double bonds [1]. Due to the cost and high toxicity of OsO<sub>4</sub> and the difficulties involved in the work-up particularly where pyridine is used, OsO<sub>4</sub> is applied catalytically with a co-oxidant, preferentially N-methylmorpholine-N-oxide(NMO). Stereoselective addition of osmium tetroxide to the sterically hindered olefins has been of research interests [2]. Use of OsO<sub>4</sub> has led to a high enantioselectivity in the hydroxylation of olefins with chiral alkaloids of cinchonane family [3].

To this end, the diols of the family of title compounds were prepared [4] and macrocyclic polyethers have been synthesized from them [5]. Herein we report the synthesis of a new triol (3).

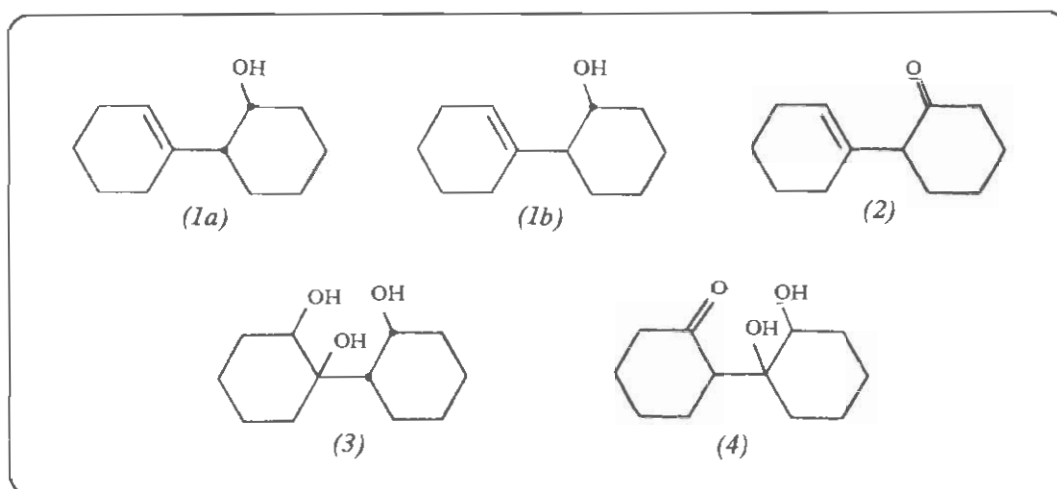
### RESULTS AND DISCUSSION

In our studies we performed the catalytic hydroxylation of cis and trans 2- cyclohexene cyclohexanol (1a, 1b) with osmium tetroxide in the presence of N- methylmorpholine-N- oxide (NMO). The results show that in this catalytic hydroxylation (OsO<sub>4</sub>/NMO), the steric factor plays an important role. Stereoelectronic control

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in osmium-catalyzed cis-dihydroxylation of 3,3-diaryl cyclopentenes recently appeared in the literature [6]. Thus for the first step we obtained 2-cyclohexene-cyclohexanone (2) by aldol condensation of cyclohexanone in the presence of  $\text{H}_2\text{SO}_4$  (60%) [7]. Treatment of (2)\* with  $\text{NaBH}_4$  in the presence of methanol furnished a mixture of (1a) and (1b) approximately in equal amounts. These two diastereomers could be separated via column chromatography using activated alumina.

When two isomers (1a) and (1b) were reacted under the same conditions using  $\text{OsO}_4$  in the presence of more than one equivalent of NMO at room temperature in acetone-water (9:1) only (1a) reacted and gave exclusively triol (3) with 67% yield. Trans isomer (1b) was found to be unchanged even after few days at room temperature. This was rationalized by means of steric repulsion of equatorial OH group which in this position reduces the activity of oxidant (NMO). The compound (3) is a triol, its structure was deduced by spectroscopic methods.

The triol (3), was also prepared by an alternative method for the first time. Compound (2) was reacted with  $\text{OsO}_4$  and more than one equivalent of NMO in the presence of acetone- $\text{H}_2\text{O}$  at room temperature which afforded (4) (81%). The reduction of diol-ketone (4) with

$\text{NaBH}_4$  in the presence of methanol gave only triol (3). In contrast with stereochemical studies on the reduction of cyclohexanone by hydride reagent, equatorial attack is more favorable. In this case it seems that the transition state is stabilized due to hydrogen bonding to tertiary OH group at the axial position (Fig. 1).

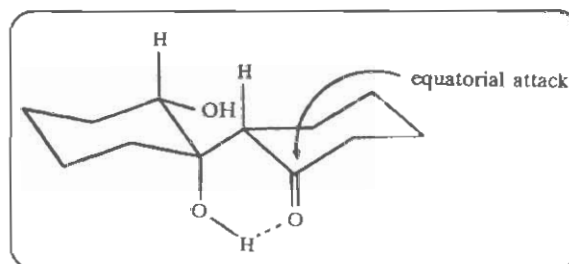


Fig. 1

## EXPERIMENTAL

Melting points were determined in a *C-Reichert* (Vienna, Austria) and are uncorrected. IR spectra were performed on FT-IR *Shimadzu-4300* (Japan). The  $^1\text{H-NMR}$  were run on *Brucker 80MHz* (Germany) using TMS as internal standard. Mass spectra were obtained on *Finigan-TSQ-70* and *Shimadzu QP-1000EX*.

A mixture of petroleum ether with a varying quantities of ether, was used as eluent. The chromatographic separation was visualized by  $\text{I}_2$  or spraying with concentrated  $\text{H}_2\text{SO}_4$ .

\* Such reduction has been previously performed with the aid of  $\text{LiAlH}_4$  in THF as solvent (see Ref. [4]).

**i) Preparation of 2-cyclohexene-cyclohexanone (2) [6]**

To 100g (1.02mole) cyclohexanon, 100g H<sub>2</sub>SO<sub>4</sub> (60%) was added dropwise in a period of 1 hour. The resulting mixture maintained at room temperature for 24 hours. Two phases were formed. The organic layer was separated and dried (Na<sub>2</sub>SO<sub>4</sub> anhyd.). The crude residue was distilled in reduced pressure and collected. 25.3g (25%) of pure product (bp<sub>8-10</sub>=147-148°C) was obtained.

IR(neat) 3060, 2800-3000, 1717, 1680, 1450cm<sup>-1</sup>.  
<sup>1</sup>H-NMR(CDCl<sub>3</sub>); δppm, 5.45(m,1H), 1.5-3.05(m, 17H).

**ii) Reduction of 2-cyclohexene-cyclohexanone (2) by NaBH<sub>4</sub>**

A solution of 4.45g (0.025mole) of (2) (freshly distilled) in 50mL of pure methanol, was treated with NaBH<sub>4</sub> (1.7g, 0.045mole) at room temperature for 3 hours and then refluxed for 2 hours. After cooling the reaction mixture was acidified by 10mL HCl (10%) and methanol was evaporated. The residue was extracted with ether and dried (Na<sub>2</sub>SO<sub>4</sub> anhyd.). The solvent was removed and, residue was chromatographed using petroleum ether-ether 80:20 over alumina (activity II-III). Two compounds were obtained: *Ia* (1.5g : 48%), *Ib* (1.6g : 52%).

*Ia*: mp= 48-50°C. R<sub>f</sub>= 0.5 (alumina, petroleum ether-ether: 80:20).

IR(KBr): 3400-3650, 3060, 1950, 1850, 1660, 1620, 1450, 900cm<sup>-1</sup>.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>/CDCl<sub>3</sub>; 2:1); δppm, 1-2.1(m, 17H), 3.44 (d, 1H, J=4Hz), 3.88(s, 1H, Broad), 5.36(1H, Broad).

MS: m/e (relative intensity) 180(6), 162(89.7), 147(19.5), 133(65.7), 119(37.7), 105(23), 91(72), 79(100), 67(58.0), 55(28.8), 43(89.7).

*Ib*: viscous liquid R<sub>f</sub>= 0.3(Al<sub>2</sub>O<sub>3</sub> eluent as *Ia*).

IR(neat): 3100-3600, 3060, 2800-3000, 1660, 1450, 1060, 1040cm<sup>-1</sup>.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>/CDCl<sub>3</sub>, 2:1); δppm, 1-2.1(m, 17H), 3.42(1H sextet); 3.79(d, 1H, J=6.4Hz), 5.39(m, 1H).

MS: m/e(relative intensity): 180(2.9), 171(2.2),

162(89.7), 147(13.2), 133(45.6), 119(25), 105(15.4), 95(25.7), 81(100), 67(26.5), 53(10.3), 41(17.6).

**iii) Reaction of *Ia* with OsO<sub>4</sub> in the presence of NMO**

To a stirred solution of cis-2-cyclohexene-cyclohexanol (*Ia*, 0.9g, 0.005mole) and 10mL acetone, were added 1.013g (0.0075mole) of NMO, 1mL of cat. OsO<sub>4</sub> solution (4% wt in H<sub>2</sub>O) and 2mL H<sub>2</sub>O. The reaction mixture was stirred for 17 hours at room temperature. The colour of mixture was green at first, after completion changed in mild brown colour which was quenched by 29g Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> and 10mL CH<sub>2</sub>Cl<sub>2</sub> and stirred for an additional 1 hour. The solvent was evaporated, residue purified via column chromatography (silicagel, 0.06-0.2, Merck, diethyl ether), 720mg of triol (3) was obtained (yield 67%).

mp= 160-162°C(C<sub>6</sub>H<sub>6</sub>).

IR(KBr): 3550-3100, 2950, 2850, 1480, 1090cm<sup>-1</sup>.

Whithout CF<sub>3</sub>CO<sub>2</sub>H

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>/CDCl<sub>3</sub>, 2:1); δppm, 1-1.9(m, 17H), 3.29(s, 1H), 3.47(covered by OH and contaminated H<sub>2</sub>O signals), 4.49(s, 1H, broad), 5.00(d, 1H, J=2Hz), 5.04(d, 1H, J=5Hz).

with one droplet of CF<sub>3</sub>CO<sub>2</sub>H

δ(ppm), 1-1.9(m, 17H), 3.47(t, 1H, J=8Hz), 4.24(s, 1H, broad).

MS: m/e(relative intensity); 214(12), 196(20.7), 178(100), 161(15), 115(2), 81(27), 4(29).

**iii) Reaction of (2) with OsO<sub>4</sub> in the presence of NMO**

To a solution of 4.225g (0.0125mole) of 2-cyclohexene-cyclohexanone (2) in 25mL acetone was added, 2.5g (0.0185mole) NMO, 2mL of solution of OsO<sub>4</sub> (4% in H<sub>2</sub>O) and 2mL H<sub>2</sub>O. The mixture was stirred for 8 hours at room temperature. After usual work-up, the residue was chromatographed (SiO<sub>2</sub> 0.01-0.6, Merck, solvent petroleum ether-ether 20:80); which yielded 2.15g (82%) diol (4). mp= 93-95°C (C<sub>6</sub>H<sub>6</sub>).

IR(KBr): 3600-3200, 2850-3000, 1710, 1700, 1450, 1060 $\text{cm}^{-1}$ .

$^1\text{H-NMR}$ (DMSO- $d_6$ /CDCl $_3$ , 2:1);  $\delta$ ppm, 1-2.4 (m, 17H), 2.8(1H, broad), 3.5(1H, broad), 3.8(1H, t, J=8Hz).

MS: m/e(relative intensity); 212(10.9), 194(68), 176(16), 148(15.8), 125(26), 114(100), 98(95), 70(56), 55(83).

#### iiii) Reduction of (4) by NaBH $_4$

To 1.5g (0.007mole) of diol ketone (4) dissolved in 25mL methanol 450mg was added (0.012mole) of NaBH $_4$  over a period of 30 min. The reaction mixture was stirred for 3 hours and refluxed for an additional 1 hour. After usual work-up water was eliminated by azeotropic distillation, the residue was chromatographed (silicagel diethyl ether) which yielded 1.1g (73%) pure product identical as triol (3).

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