HYDROGENOLYSIS BY LITHIUM ALUMINIUM HYDRIDE – ALUMINIUM CHLORIDE OF ETHER SOLUTIONS OF CAMPHOR ETHYLENE KETAL AND NORCAMPHOR ETHYLENE KETAL

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W. W. ZAJAC, JR.,¹ B. RHEE, AND R. K. BROWN Department of Chemistry, University of Alberta, Edmonton, Alberta Received March 3, 1966

ABSTRACT

The lithium aluminium hydride – aluminium chloride reductive cleavage of norcamphor ethylene ketal yields 2-(2-endo-norbornyloxy)ethanol in $\geq 98\%$ yield, whereas the similar reduction of camphor ethylene ketal gives 2-(2-isobornyloxy)ethanol in 78% yield and 2-(2-bornyloxy)ethanol in 22% yield. These are the products arising from steric approach control.

INTRODUCTION

As part of an investigation of the hydrogenolysis of acetals and ketals (1-3), we have examined the reductive cleavage by lithium aluminium hydride – aluminium chloride of ether solutions of the ethylene ketals of norcamphor and camphor. This paper describes the results of this work.

RESULTS AND DISCUSSION

The hydrogenolysis of norcamphor ethylene ketal, I, by the mixed reagent LiAlH₄-AlCl₃ was carried out according to the published procedure (3). Of the two isomeric products (IIa and IIb, Reaction Scheme 1) which may result from this cleavage, the 2-(2-endo-norbornyloxy)ethanol, IIa, was the exclusive product. This was proven by independent syntheses of both IIa and IIb as well as by degradation of the hydrogenolysis product, II, to 2-norborneol by a method which avoided isomerization of the 2-norborneol so formed.



REACTION SCHEME 1. a = endo isomer and b = exo isomer in each case. ¹On sabbatical leave from Villanova University, Villanova, Pennsylvania, U.S.A. Canadian Journal of Chemistry. Volume 44 (1966)

1547

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1548

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The synthesis of the two possible reduction products, IIa and IIb, was accomplished by lithium aluminium hydride reduction of the ethyl esters of 2-endo- and 2-exo-norbornyloxyacetic acid (IIIa and IIIb). The latter were prepared by reaction of the sodium salt of authentic 2-endo- and 2-exo-norborneol, IVa and IVb, with ethyl bromoacetate. Unfortunately, neither the isomeric esters IIIa and IIIb nor the hydroxyethers IIa and IIb could be separated by gas-liquid chromatography² using a variety of conditions and columns. However, the nuclear magnetic resonance spectra of the hydroxyethers IIa and IIb were sufficiently different to be clearly distinguishable. An examination of the nuclear magnetic resonance spectrum of the reduction product of the ketal I showed that most, if not all, of the hydrogenolysis product had the endo configuration IIa. Compounds IIa and IIb show complex absorptions in the τ 8–9 region caused by the ring protons on carbons 3, 5, 6, and 7. The carbon 2 proton (endo or exo) absorbs in the τ 5.8–6.0 region but its identification is obscured by the absorption of the methylene protons ($-OCH_2CH_2O-$), which absorb in the same region. However, for the endo compound IIa, the bridgehead protons on carbon 1 and carbon 4 give rise to two unresolved multiplets centered at τ 7.63 and τ 7.87 with half-widths of 8 c.p.s. and 11 c.p.s., respectively. The exo compound gives rise to only one unresolved multiplet centered at τ 7.83 with a half-width of 14 c.p.s.

To determine if a significant amount of the *exo* hydroxyether IIb had actually been formed but been missed in the analytical method employed, the hydrogenolysis product II was degraded to the alcohol(s) IV, which are known to be separable quantitatively by gasliquid chromatography (4-8). The key step in the degradation sequence was the elimination of the 2-norbornyloxy group from the bromoether VI with either magnesium (9) or *n*-butyllithium (10). That the degradation sequence of reactions truly reflects the proportion of *endo* isomer in the reduction product II was established by subjecting a synthetic mixture of known amounts of the *endo* and *exo* hydroxyethers II to the degradation reaction sequence. The proportion of *endo* and *exo* norborneols obtained agreed within $\pm 2\%$ of the proportion of *endo* and *exo* hydroxyethers in the synthetic starting mixture. The conditions of the degradation also exclude the possibility of a change in the configuration of the norborneol formed. Authentic *exo* or *endo* alcohol (IV) was found to remain unchanged under similar reaction conditions.

The product of the degradation of the material obtained by hydrogenolysis of the ketal I was shown by gas-liquid chromatography to consist of only one substance, identical in all respects with 2-endo-norborneol (IVa). Hence, the LiAlH₄-AlCl₃ reductive cleavage of the ketal I produces $\geq 98\%$ of the endo hydroxyether IIa.

The hydrogenolysis of the ethylene ketal of camphor was carried out in the same manner as that for the norcamphor ketal. Degradation of the reduction product (VIII) was accomplished by the same reaction sequence as employed for II, i.e. VIII \rightarrow IX \rightarrow X \rightarrow XI (Reaction Scheme 1). The borneol (XIa) and isoborneol (XIb) could also be analyzed quantitatively by gas-liquid chromatography (4, 5, 8, 11, 12). According to the results obtained from the degradation, the product of the reduction of the ethylene ketal of camphor is a mixture of 78 \pm 2% of the hydroxyether with the *exo* configuration (VIIIb) and 22 \pm 2% of the hydroxyether with the *endo* configuration (VIIIa).

The preceding results permit the conclusion that the hydride species enters from the least hindered side of the ketals I and VII. Since the hydroxyethers obtained from the $LiAlH_4$ -AlCl₃ reductive cleavage of cyclic acetals and ketals are stable to our reaction conditions (1–3 and references therein), we are dealing with a case of steric approach

²Although the individual, pure isomers IIa and IIb showed slightly different retention times (ca. 0.2 min) under some conditions, mixtures of the two isomers gave only one broad peak.

ZAJAC ET AL.: HYDROGENOLVSIS

control. The hydrogenolysis reactions studied in this investigation are analogous to the reduction of norcamphor and camphor to 2-norborneol (>90% endo isomer) and isoborneol (i.e. the exo isomer, >80%), respectively, with LiAlH₄ alone (5, 13, 14) or with $LiAlH_4$ in the presence of AlCl₃ (8) under kinetically controlled conditions, in that the course of reaction is governed by steric approach control (15).

This work presents a clear case in which steric factors are of predominant importance in controlling the approach of the *reducing species* during the hydrogenolysis of acetals and ketals (cf. refs. 16-18).

EXPERIMENTAL

All boiling points and melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer model 421 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 spectrometer with tetramethylsilane as an internal standard. In all cases the integrated nuclear magnetic resonance spectra were consistent with the assigned structures of the compounds. Gas chromatographic analysis was carried out on an Aerograph model A-700 instrument with a 20 ft by $\frac{1}{4}$ inch column packed with 25% Carbowax 20M on Gas Chrom P.

Norcamphor ethylene ketal was synthesized in 91% yield from norcamphor and ethylene glycol according to the method of Salmi (19), b.p. 78–80° at 14 mm, η_D^{25} 1.4319. Anal. Calcd. for C₉H₁₄O₂: C, 70.09; H, 9.15. Found: C, 69.65; H, 8.52.

Camphor ethylene ketal was synthesized in 67% yield from camphor and ethylene glycol according to the method of Salmi (19), b.p. 64° at 1.5 mm, yD²⁵ 1.4770.

Anal. Calcd. for C12H20O2: C, 73.43; H, 10.27. Found: C, 73.47; H, 10.08.

Ethyl (2-exo-norbornyloxy) acetate was synthesized in 50% yield from 2-exo-norborneol, sodium hydride, and ethyl bromoacetate in benzene according to the procedure of Leffler and Calkins (20), b.p. 77° at 1 mm, ηp^{25} 1.4162

Anal. Calcd. for C11H18O3: C, 66.64; H, 9.15. Found: C, 66.46; H, 9.04.

Ethyl (2-endo-norbornyloxy) acetate was synthesized in 53% yield from 2-endo-norborneol, sodium hydride, and ethyl bromoacetate in benzene according to the procedure of Leffler and Calkins (20), b.p. 80° at 1 mm, $\eta D^{25} 1.4160$

Anal. Calcd. for C₁₁H₁₈O₃: C, 66.64; H, 9.15. Found: C, 66.42; H, 8.93.

2-(2-exo-Norbornyloxy)ethanol was synthesized in 60% yield by the reduction of the exo ester with lithium aluminium hydride in ether (21), b.p. 71° at 1 mm, $_{7D}^{25}$ 1.4812. Anal. Calcd. for C₉H₁₆O₂: C, 69.19; H, 10.13. Found: C, 68.55; H, 10.08.

2-(2-endo-Norbornyloxy)ethanol was synthesized in 67% yield by the reduction of the endo ester with lithium aluminium hydride in ether (21), b.p. 72° at 1 mm, η_D^{25} 1.4815.

Anal. Calcd. for C₉H₁₆O₂: C, 69.19; H, 10.13. Found: C, 69.17; H, 10.26.

This compound is identical with the hydrogenolysis product of norcamphor ethylene ketal.

Hydrogenolysis of Norcamphor Ethylene Ketal

This was carried out with lithium aluminium hydride and aluminium chloride in ether according to the method of Leggetter and Brown (1). The product was obtained in 95% yield. The tosylate of the reduction product was synthesized in 95% yield from p-toluenesulfonyl chloride in pyridine according to the method of Wiberg and Lowry (22), m.p. 49-51°.

Anal. Calcd. for C16H22O4S: C, 61.91; H, 7.13. Found: C, 61.75; H, 7.06.

The p-toluenesulfonate was converted into the bromide with lithium bromide in acctone according to the method of Wiberg and Lowry (22). The bromide was used without further purification (98% purity by gasliquid chromatography).

Degradation of Norcamphor Ethylene Ketal Reduction Product

(a) Grignard Method

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The bromide (9.0 mmoles) in 100 ml of ether was added dropwise to a mixture of ether and magnesium turnings (9.0 mmoles). The reaction mixture was heated under reflux for 20 h. The mixture was cooled in an ice bath, and 30 ml of 2% ammonium chloride solution was added dropwise. The ether layer was removed and combined with the ether extracts of the aqueous phase. The dried (MgSO₄) ether solution was concentrated, whereupon the residue solidified. The residue was dissolved in a small quantity of chloroform and analyzed by gas-liquid chromatography, at a column temperature of 130° and a helium flow rate of 190 ml/min. The retention time of the product 2-endo-norborneol was 24.4 min. 2-exo-Norborneol had a retention time of 22.6 min under identical conditions. The only other product present in the reaction mixture was unreacted starting material, to the extent of 37%.

(b) n-Butyllithium Method

In a nitrogen atmosphere, 5 ml of a solution of 15% n-butyllithium in hexane was added dropwise to a stirred solution of 8.2 mmoles of the bromide in 50 ml of ether. The solution was stirred overnight, and 30 ml of ice water was added cautiously. The ether layer was separated and combined with the ether extracts of the aqueous phase. The dried (MgSO₄) ether solution was concentrated, whereupon the residue solidified. The residue was dissolved in a small quantity of chloroform and analyzed by gas-liquid chromatography as described above. The major product was 2-endo-norborneol. Unreacted starting material was present to the extent of 13%.

Hydrogenolysis of Camphor Ethylene Ketal

This was carried out with lithium aluminium hydride and aluminium chloride in ether according to the procedure of Leggetter and Brown (1). The product was obtained in 93% yield, b.p. 75-77° at 1.5 mm. Anal. Calcd. for C12H22O2: C, 72.68; H, 11.18. Found: C, 73.20; H, 11.00.

The tosylate of the reduction product was prepared according to the method of Wiberg and Lowry (22) in 98% yield. This was converted into the bromide (yield 95%) according to published directions (22). The bromide was treated with n-butyllithium according to the procedure described above for the degradation of the norcamphor ethylene ketal reduction product. The reaction mixture was subjected to gas-liquid chromatographic analysis, at a column temperature of 150° and a helium flow rate of 90 ml/min. The retention time of isoborneol was 32.6 min, and of borneol 36.2 min. The product consisted of 78% isoborneol and 22% borneol. Unreacted starting material was present to the extent of 11%.

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