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REACTIONS OF 3,4-EPOXY ALCOHOLS. NEW RESULTS

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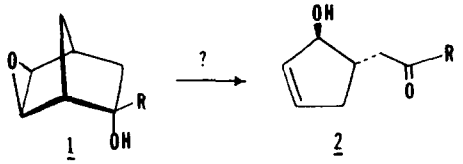
Abstract: The treatment of 5,6-epoxynorbornan-2-ol derivatives with acidic or basic reagents has provided new examples of oxetane formation, particularly a novel dimerization and a cyclization following reversible first order kinetics.

Recent interest in the chemistry of 3,4-epoxy alcohols has centered on applications toward the synthesis of the taxane ring system,[1] on models for the biosynthesis of secolongifolene[2] and the antitumor xanthanolides,[3] and on studies relating to the structural effects governing the formation of oxetanes[4] and fragmentation products.[5] Our interest in 3,4-epoxy alcohols stems from the possible fragmentation of the 2-hydroxy-5,6-epoxybicyclo[2.2.1] heptane system(1) to an intermediate 2 of potential use in the synthesis of prostaglandin analogs.[6] Indeed, the near trans coplanar geometry of the bonds

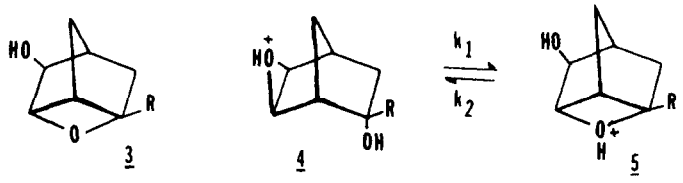


1 2

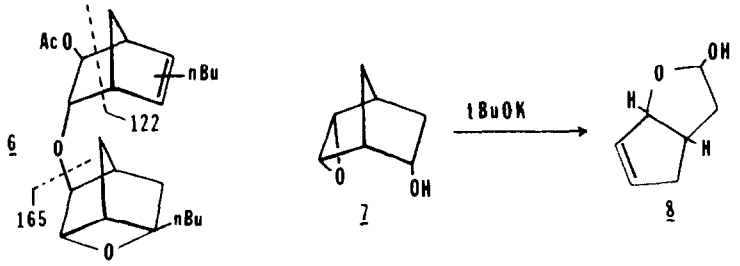
in 1 involved in the elimination, the relief of strain at the tertiary hydroxyl center, and the formation of a carbonyl group might all contribute to facilitate a 1 to 2 fragmentation.

2-endo-Hydroxy-2-exo-n-butyl-5,6-epoxybicyclo[2.2.1]heptane(1, R=nBu)[7] was prepared from dehydronorcamphor[8] by reaction with nBuMgBr in ether followed by mCPBA/CH_2Cl_2. The stereochemistry of 1 follows from the established exo attack of Grignard reagents on dehydronorcamphor,[9] the known exo epoxidation of endo-5-norbornen-2-ol,[10] a comparison of the NMR spectrum of 1 with that of analogous exo epoxides,[11] and the subsequent reaction of 1 to form an oxetane in high yield. 3,4-Epoxy alcohol 1(R=nBu) was treated with potassium t-butoxide in t-butyl alcohol at room temperature for 4 days

whereupon the oxetane 3(R=nBu) was formed in 90% yield.[12] No fragmentation product 2 was observed in the NMR spectrum of the crude product. Oxetane 3 (R=nBu) was also slowly produced when 1 was reacted with o-chlorobenzoic acid (18 mol %) in CCl_4. The kinetics of this reaction were followed over 3 half-lives by NMR. A reversible first order process[13](correlation coeff.=0.9985) was observed($t_{\frac{1}{2}}$ = 1.66 days, $k=k_1+k_2=0.42$ days^{-1}, Keq=0.39). By implication, the rate-determining step in the protonated species 4 ⇌ 5(R=nBu). Apparently C-O cleavage in 5 to give the tertiary carbocation at C-2 either does not occur in the non-polar solvent, or is reversible and rapid with respect to 4 ⇌ 5.



Compound 1(R=nBu) also reacts with a strong acid solution. Treatment of a 0.72 M solution of 1 in acetone with pTsOH(14 mol %) led to a rapid disappearance of the epoxy protons in the NMR and the appearance of new carbinol signals at 4.18 and 4.67 ppm. After work-up, the crude reaction product was acetylated(Ac_2O/pyridine) to produce a 34% yield (from 1) of a product whose spectral data are consistent with 6. The CI-MS of 6 shows the

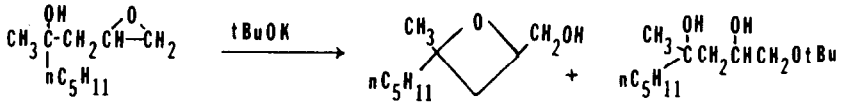


pseudomolecular ion at m/z 389(base peak)$(M + H)^{\cdot +}$ along with 329(67%)(loss of HOAc). The molecular ion is not seen in the EI-MS, but intense fragment ions at m/z 165(21%)(C-O cleavage), 122(34%)(retro Diels-Alder), and 43(base peak) ($CH_3CO^{\cdot +}$) define the features of 6. The IR spectrum shows absorption at 1742 and 1220 cm^{-1}(acetate) along with 950 cm^{-1}(oxetane).[10] The NMR spectrum, although complex, is consistent with the proposed dimer 6. Similar dimerizations of non-cyclic 3,4-epoxy alcohols are known.[4]

2-endo-Hydroxy-2-exo-phenyl-5,6-epoxybicyclo[2.2.1]heptane(1, R=C_6H_5) was also prepared from dehydronorcamphor by Grignard addition of PhMgBr followed by mCPBA/CH_2Cl_2 epoxidation. Reaction of 1(R=C_6H_5) with potassium t-butoxide/

t-butyl alcohol gave the corresponding oxetane 3 as an unstable oil.

At this point in our work, Holton and Kennedy reported the rapid fragmentation of the endo-5,6-epoxide 7 with potassium t-butoxide to give lactol 8(100% yield) and suggested a general preference for syn coplanar elimination in 3,4-epoxy alcohol fragmentations.[14] The failure of our tertiary alcohols(anti geometry) to fragment is consistent with this proposal. In addition, we have investigated other examples where syn coplanar geometry can be approached by bond rotation in non-rigid systems. cis-3,4-Epoxy-cyclopentan-1-ol,[15] in its hydrogen bonded conformation, is such a compound, and fragmentation here might provide a model for xanthanolide biosynthesis.[3] However, only recovered starting material or polymerizations were observed under a variety of acidic and basic conditions. Isopulegol epoxide gave only recovered starting material after long exposure to potassium t-butoxide/ t-butyl alcohol. Finally, a similar treatment of 1,2-epoxy-4-hydroxy-4-methyl-nonane(9) gave only the oxetane 10(5.6%)[4] and the t-butyl alcohol adduct 11(40%).[7,12]



9 10 11

In conclusion, we report herein new results regarding the chemistry of 3,4-epoxy alcohols, observations in accordance with Holton's recent hypothesis (vide ante).[14]

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