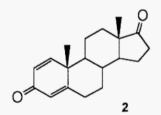
EPOXIDATION OF 1,4-DIENYL 3-KETO STEROIDAL COMPOUNDS BY DIMETHYLDIOXIRANE: KINETICS

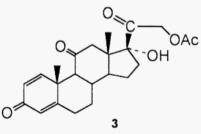
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Abstract. The epoxidation of 1,4-dienyl 3-keto steroidal compounds by dimethyldioxirane yields monoepoxides as the primary products as reported in the literature. Kinetic data show the 1,4-dienyl 3-keto system to be at least ten fold more reactive than simple α , β -unsaturated systems.

Introduction

For the last couple of decades, dioxiranes have been investigated extensively as powerful oxidants.¹ Dimethyldioxirane, **1**, whether generated *in situ*² or isolated³ in acetone solution, is known to be a highly selective and stereospecific oxygen-atom transfer reagent.⁴ Because of the mild reaction conditions and the ease of product purification, dimethyldioxirane is often the reagent of choice for the epoxidation of carbon-carbon double bonds. The reaction has been shown to occur via an electrophilic concerted pathway⁴ with a *'spiro'* transition state.⁵ Recently, kinetic results for epoxidation of simple α , β -unsaturated carbonyl compounds including related steroids have been reported.⁶ The product studies for the epoxidation of α , β -unsaturated steroids by **1** had been reported earlier.⁷ Interestingly, the epoxidation by dimethyldioxirane of 1,4-dienyl 3-keto steroidal compounds has shown^{7b} unique regioselectivity. In certain cases with a carbonyl group at C₁₁ dioxirane epoxidation yielded^{7b} the unexpected 1 α , 2 α epoxide (attack at the less nucleophilic double bond). For the remainder of the 1,4-dienyl 3-keto type compounds, dioxirane attack was reported to occur at the more nucleophilic double bond but preferentially from the β -side.^{7b} This is in contrast to preferential α -attack of dimethyldioxirane on steroids like 4-cholesten-3-one and progesterone.⁷ We report here a kinetics study of the reaction of dimethyldioxirane 1 with (+)-androsta-1,4-diene-3,17-dione **2** and prednisone acetate **3**.

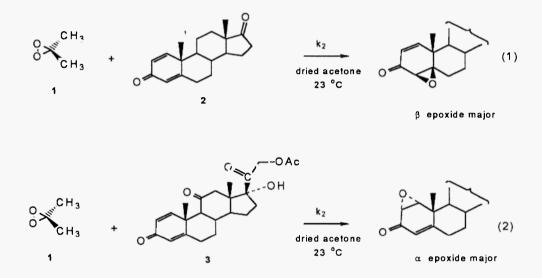




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Results and Discussion

Epoxidation of 1,4-dienyl 3-keto type steroids⁸ (+)-androsta-1,4-diene-3,17-dione **2**, and **21**acetoxy-17 α -hydroxy-1,4-pregnadiene-3,11,20-trione (prednisone acetate) **3** with an excess of dimethyldioxirane **1** at room temperature afforded mixtures of monoepoxides, in excellent yield in agreement with the published results.^{7b} The products were isolated and characterized by ¹H NMR spectroscopy. Comparison of ¹H NMR data with the reported supplementary spectra^{7b} showed that the major product for epoxidation of **2** was the β -epoxide shown in reaction 1 (81 ± 5% yield) while the major product for **3** was the α -epoxide (73 ± 5%; reaction 2).



Kinetics studies for the epoxidation of 1,4-dienyl 3-keto-unsaturated steroids 2 and 3 by dimethyldioxirane were performed using UV techniques at 380 nm.⁹ The kinetics experiments were carried out under pseudo first order conditions with at least a 10:1 substrate to dioxirane ratio in dried acetone. The k_2 values were determined at 23 °C and are the average of at least three independent runs. GC/MS studies were conducted on the kinetics solutions after epoxidation to confirm that oxidation had taken place. The kinetic data for 2 and 3 as well as those from the literature for model compounds progesterone 4 and phorone 5 are listed in Table 1.

The results (Table 1) show that the relative rate constants for epoxidation of 1,4-dienyl 3-keto compounds 2 and 3 were 10- and 23-fold greater than that for the steroid α , β -unsaturated carbonyl model compound 4. The only reported^{6a} kinetics result for a 1,4-dienyl 3-keto system is on the acyclic compound 5 (phorone) which is 2 to 5-fold less reactive than the related steroidal systems. Presumably, the increased reactivity of the 1,4-dienyl 3-keto systems with respect to simple α , β -unsaturated carbonyl

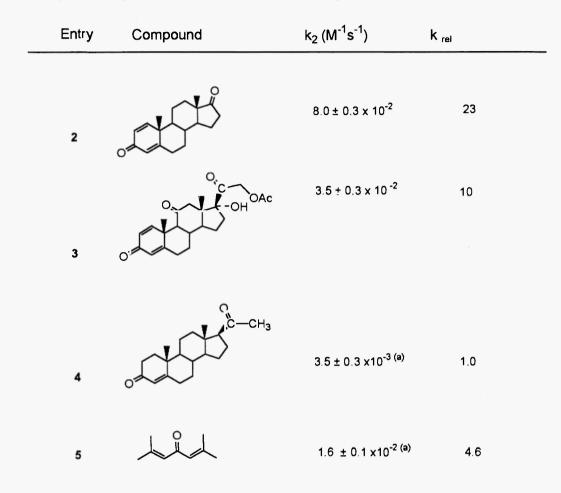


Table 1. Second order rate constants for the mono-epoxidation of 1,4-dienyl 3-keto steroids 2 and 3 and model systems progesterone 4 and phorone 5 by dimethyldioxirane at 23 °C in acetone solution.

Compounds 4 and 5 are included for comparison, taken from ref. 6b and 6a, respectively.

compounds is due to cross conjugation which should increase the electron density on the "alkenes." The increased reactivity of **2** relative to **5** appears to be due to the decreased steric interactions in the cyclic systems. The approximate 2-fold difference in relative reactivity between compounds **2** and **3** can be rationalized to be due to the electron withdrawing effect of the carbonyl at C₁₁. In simple α , β -unsaturated unsaturated carbonyl systems the presence of a remote carbonyl group one carbon closer was found^{6b} to result in a **4**-fold decrease in relative reactivity.

In steroids with a simple α , β -unsaturated carbonyl group such as in progesterone 4, an α epoxide/ β -epoxide ratio of 4 was obtained. Preference for α -attack by dioxirane 1 on this type of system was explained^{6b.7a} due to the presence of the angular methyl group β at position 8a. Clearly this explanation is not sufficient to explain the results for 2. The more nucleophilic position in 2 underwent epoxidation but attack was preferentially from the β -side. The presence of the additional site of unsaturation apparently has decreased the steric interactions. The result for **3** in which the less nucleophilic site is attacked preferentially from the α -side is more difficult to explain. The dipole-dipole interaction model suggested^{7b} by Boricelli and Lupattelli based on product studies appears to be the best explanation.

In summary, fused polycyclic 1,4-dienyl 3-keto systems are considerably more reactive than simple α,β -unsaturated systems toward epoxidation by dimethyldioxirane. Steric influences are reduced in compounds leading to β -side attack at the more nucleophilic position. The origin of α -side attack in selected compounds is not clear.

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- Compound 2 was commercially available. Compound 3 was prepared by modification of 17α-21dihydroxy-1,4-pregnadiene-3,11,20-trione upon treatment with Ac₂O/Py as described by B.A. Brady, M. Geoghegan and W.I. O'Sullivan, J. Chem. Soc., Perkin Trans. 1, 1557 (1989)
- 9. Due to interference from absorption by substrates, the change in dioxirane concentration was monitored at 380 nm rather than at the usual wavelength of 330 nm.

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