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

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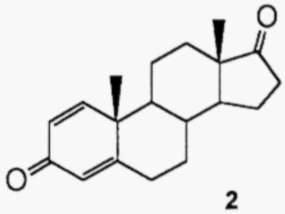
Abstract. The epoxidation of 1,4-dienyl 3-keto steroidal compounds by dimethyldioxirane yields mono-epoxides as the primary products as reported in the literature. Kinetic data show the 1,4-dienyl 3-keto system to be at least ten fold more reactive than simple α,β-unsaturated systems.

Introduction

For the last couple of decades, dioxiranes have been investigated extensively as powerful oxidants.[1] Dimethyldioxirane, **1,** whether generated *in situ*[2] or isolated[3] 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 pathway[4] 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 C_{11} dioxirane epoxidation yielded[7b] the unexpected 1α, 2α 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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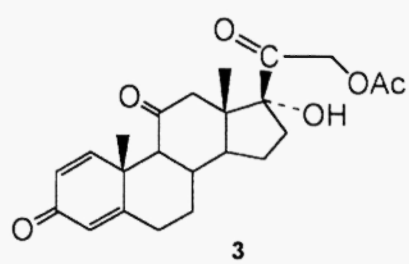

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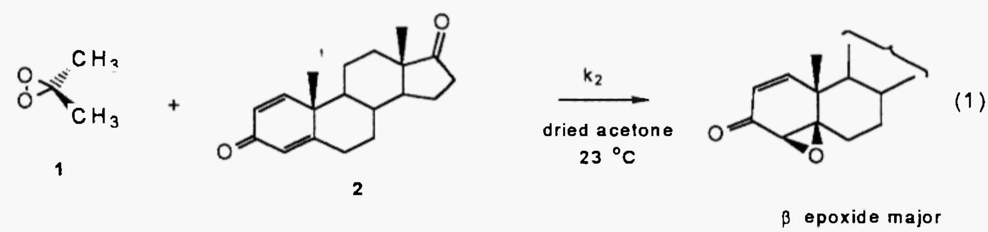
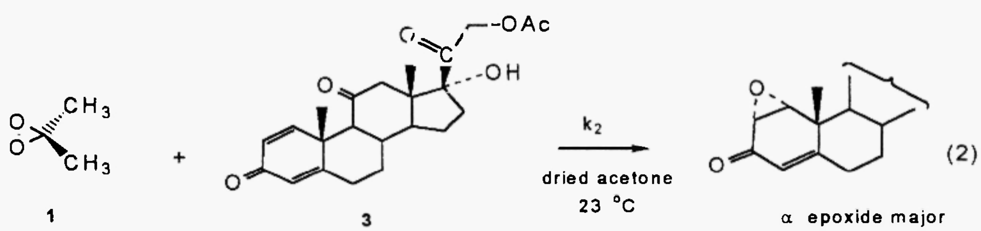
Results and Discussion

Epoxidation of 1,4-dienyl 3-keto type steroids[8] (+)-androsta-1,4-diene-3,17-dione **2**, and 21-acetoxy-17α-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 ^{1}H NMR spectroscopy. Comparison of ^{1}H 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).

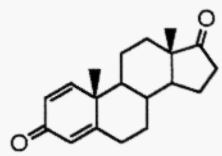
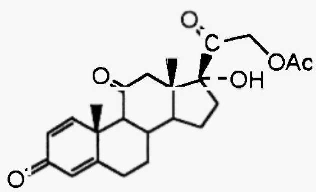
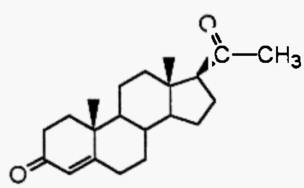
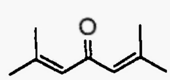




Kinetics studies for the epoxidation of 1,4-dienyl 3-keto-unsaturated steroids **2** and **3** by dimethyldioxirane were performed using UV techniques at 380 nm.[9] The kinetics experiments were carried out under pseudo first order conditions with at least a 10:1 substrate to dioxirane ratio in dried 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.

Entry	Compound	k_2 ($M^{-1}s^{-1}$)	k_{rel}
2		$8.0 \pm 0.3 \times 10^{-2}$	23
3		$3.5 \pm 0.3 \times 10^{-2}$	10
4		$3.5 \pm 0.3 \times 10^{-3}$ (a)	1.0
5		$1.6 \pm 0.1 \times 10^{-2}$ (a)	4.6

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 C_{11}. 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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References and Notes

1. For reviews see: a) R. Curci in A.L. Baumstark (Ed.), Advances in Oxigenated Process, Vol. 2, JAI, Greenwich, CT, 1990, Chapter I, p 1; b) E.L. Clennan, Trends in Organic Chemistry, **5**, 231 (1995); (c) W. Adam, C.R. Saha-Moeller and P.A. Ganeshpure, Chem. Rev. **101**, 3499 (2001)
2. a) P.A. Ganeshpure and W. Adam, Synthesis, 179 (1996); b) S.E. Denmark and Z. Wu, Synlett, S1, 847 (1999)
3. a) R.W. Murray and R. Jeyaraman, J. Org. Chem. **50**, 2847 (1985); b) R.W. Murray and R. Jeyaraman, J. Org. Chem. **52**, 746 (1987)
4. a) A.L. Baumstark and P.C. Vásquez, J. Org. Chem. **53**, 3437 (1988); b) R.W. Murray and D.L. Shiang, J. Chem. Soc., Perkin Trans. 2, 349 (1990); c) A.L. Baumstark and D.B. Harden, J. Org. Chem. **58**, 7615 (1993)
5. A.L. Baumstark and C.J. McCloskey, Tetrahedron Lett. **28,** 3311 (1987)
6. a) A.L. Baumstark, H. Chen, S.N. Singh and P.C. Vásquez, Heterocycl. Commun., **6**, 501 (2000); b) A.M. Navarro-Eisenstein, P.C. Vasquez, P.J. Franklin and A.L. Baumstark, *ibid*, **9**, in press (2003)
7. a) P. Bovicelli, P. Lupattelli, E. Mincione, T. Prencipe and R. Curci, J. Org. Chem. **57**, 2182 (1992); b) P. Bovicelli and P. Lupattelli, *ibid*, **39**, 4304 (1994)
8. Compound **2** was commercially available. Compound **3** was prepared by modification of 17α-21-dihydroxy-1,4-pregnadiene-3,11,20-trione upon treatment with Ac_2O/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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