The Transannular Effect of One Androstane Epoxide on the Stereochemistry of a Second Epoxidation

J. Chem. Research (S), 1999, 538–539
J. Chem. Research (M), 1999, 2365–2383

James R. Hanson,* Peter B. Hitchcock and Ismail Kiran

The School of Chemistry, Physics and Environmental Science, The University of Sussex, Brighton, Sussex, BN1 9QJ UK

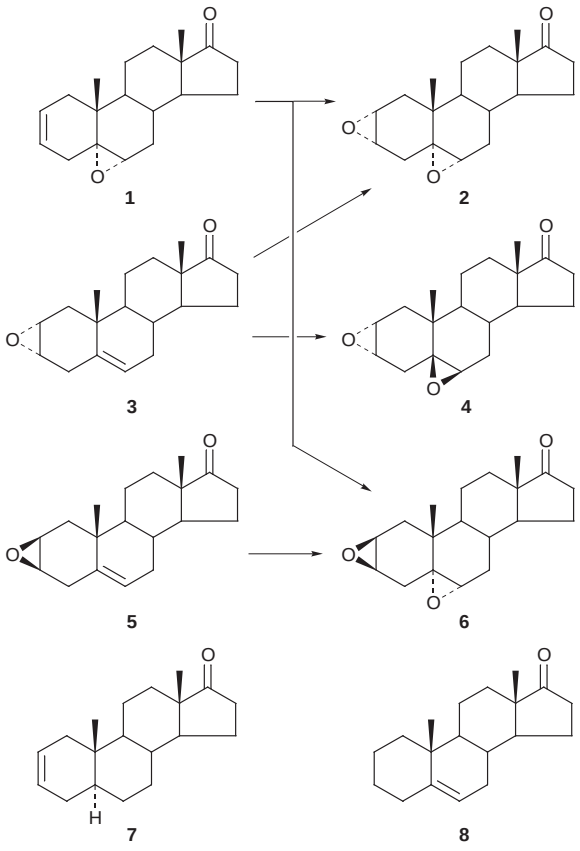
The transannular directing effect of a 2α,3α-, 2β,3β- and 5α,6α-epoxide on the epoxidation of a 5-ene and a 2-ene, respectively, is shown to increase the proportion of epoxidation of the *anti* face of the alkene when compared to the unsubstituted 2- and 5-androstenes.

The facial selectivity in the epoxidation of steroidal alkenes arises from the combination of the stereochemical requirements of the interaction between the π-HOMO of the alkene and the σ*-LUMO of the O–O bond of the peracid reagent and the stereochemical directing effects of the steroid skeleton. These include the steric hindrance of the C-10β methyl group and neighbouring group effects such as those of an allylic hydroxy group.[1–4] The formation of 4β,5β:6α,7α-diepoxides by epoxidation of androsta-4,6-dienes with *m*-chloroperbenzoic acid has been rationalized[5] in terms of the directing effect of one epoxide on the facial selectivity of the second epoxidation. Once the initial epoxide has been formed, repulsive interactions between the non-bonding electrons of the first epoxide and the π-electron cloud of the adjacent alkene could influence the facial selectivity of the second epoxidation by increasing the electron density on the face of the alkene that is *trans* to the first epoxide. The overall stereochemistry of epoxidation of a steroidal conjugated diene would then be a balance between this effect and the stereochemical directing effect of the angular methyl group and other neighbouring groups. We have now examined the epoxidation of 5α,6α-epoxyandrost-2-en-17-one **1**,[6] 2α,3α-epoxyandrost-5-en-17-one **3**,[7] and 2β,3β-epoxyandrost-5-en-17-one **5**.[7] In these homoallylic epoxyalkenes it is possible to examine the influence of the stereochemistry of one epoxide on the second epoxidation by comparing the results with those of the unsubstituted androst-2-en-17-one **7** and androst-5-en-17-one **8**.

The epoxidation of the alkenes **7** and **8** is dominated by the directing effect of the C-10β methyl group leading to attack on the α-face.[8,9] In our hands, epoxidation of androst-2-en-17-one **7** with *m*-chloroperbenzoic acid in chloroform gave entirely the 2α,3α-epoxide, with no detectable amount of the β-epoxide. Epoxidation of androst-5-en-17-one **8** gave a 7:3 ratio of the α:β-epoxides based on the relative integrals of the δ_H 2.92/3.07 signals.[10,11]

Epoxidation of 5α,6α-epoxyandrost-2-en-17-one **1** gave a separable 3:1 mixture of 2α,3α:5α,6α-diepoxyandrostan-17-one **2** and 2β,3β:5α,6α-diepoxyandrostan-17-one **6**. The stereochemistry of the latter was established by X-ray crystallography (Fig. 1). Epoxidation of 2α,3α-epoxyandrost-5-en-17-one **3** gave a 2:1 mixture of the 2α,3α:5α,6α- and 2α,3α:5β,6β-epoxides **2** and **4**, the stereochemistry of which were assigned by a combination of spin decoupling and nuclear Overhauser effect experiments. Epoxidation of 2β,3β-epoxyandrost-5-en-17-one **5** gave entirely (89% yield) the 2β,3β:5α,6α-epoxide **6**.

These results show that there is a stereochemical directing effect from the 5α,6α-epoxide on the epoxidation of the 2-ene and a smaller effect of the 2,3-epoxides on the epoxidation of a 5-ene leading to a greater proportion of attack on the opposite face compared to the unsubstituted steroid. The possibility that this was because the 5α,6α-epoxide constrained ring A to adopt a different conformation was excluded by a comparison of the X-ray crystal structure of 5α,6α-epoxyandrost-2-en-17-one (Fig. 2) with that of 17β-chloroacetoxy-5α-androst-2-ene.[13] There



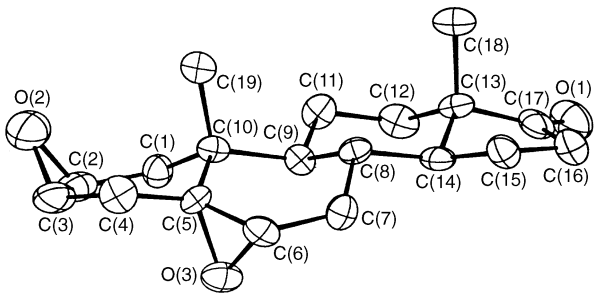


Fig. 1 X-Ray crystal structure of compound **1**

* To receive any correspondence.

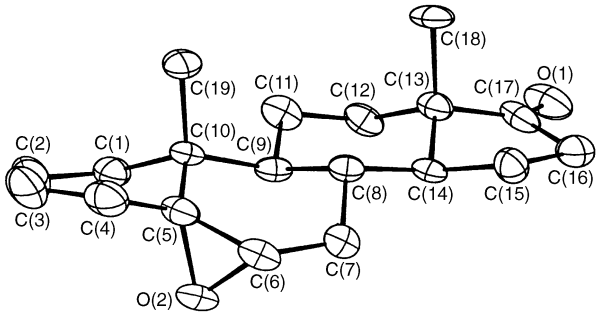


Fig. 2 X-Ray crystal structure of compound **2**

did not appear to be any significant differences although the conformation of ring B was obviously different. Bearing in mind the distances and angles involved, these effects are therefore probably steric rather than electronic in origin.

Crystallographic Data and Structure Determinations.— Compound **1**: $C_{19}H_{26}O_2$, $M_r = 286.4$, monoclinic, space group $P2_1$ (no. 4), $a = 9.332(10)$, $b = 6.305(9)$, $c = 13.614(7)$ Å, $\beta = 102.71(6)^\circ$, $V = 781(2)$ A^3, $Z = 2$, $\mu = 0.66\,mm^{-1}$. A total of 1144 reflections were collected for $2 < \theta < 55^\circ$ and $0 < h < 9$, $0 < k < 6$, $-14 < l < 14$. 933 Reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods using SHELXS-93[15] and refined using SHELXL-97.[16] The final R indices were $R_1 = 0.066$, $wR_2 = 0.164$ and R indices (all data) $R_1 = 0.076$, $wR_2 = 0.177$.

Compound **6**: $C_{19}H_{26}O_3$, $M_R = 302.4$, monoclinic, space group $P2_1$ (no.4), $a = 7.998(2)$, $b = 6.642(2)$, $c = 15.285(2)$ Å, $\beta = 100.23(2)^\circ$, $V = 799.1(3)$ A^3, $Z = 2$, $\mu = 0.66\,mm^{-1}$. A total of 979 reflections were collected for $2 < \theta < 50^\circ$ and $0 < h < 7$, $0 < k < 6$, $-15 < 1 < 14$. 702 Reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods using SHELXS-93[15] and refined using SHELXL-97.[16] The final R indices were $R_1 = 0.053$, $wR_2 = 0.123$ and R indices (all data) $R_1 = 0.076$, $wR_2 = 0.137$

Tables of atomic co-ordinates, bond lengths and angles, anisotropic displacement factors and hydrogen atom coordinates are given in the appendix.

I. K. wishes to thank the Turkish Government for financial assistance.

Techniques used: ^{1}H NMR, IR, X-ray crystallography

References: 16

Appendix: Crystallographic data for compounds **1** and **6**.

Received, 13th April 1999; Accepted, 2nd June 1999
Paper E/9/02935D

References cited in this synopsis

1 K. W. Woods and P. Beak, *J. Am. Chem. Soc.*, 1991, **113**, 6281.
2 D. N. Kirk and M. P. Hartshorn, *Steroid Reaction Mechanisms*, Elsevier, Amsterdam, 1968, p. 71.
3 H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958.
4 M. Mousseron-Canet and J. C. Guilleux, *Bull. Soc. Chim. Fr.*, 1966, 3853.
5 J. R. Hanson, P. B. Hitchcock and I. Kiran, *J. Chem. Res.*, 1999, (*S*) 198; (*M*) 1082.
6 T. D. Organ and J. R. Hanson, *J. Chem. Soc. C*, 1970, 2473.
7 M. M. Campbell, R. C. Craig, A. C. Boyd, I. M. Gilbert, D. S. Savage and T. Sleigh, *J. Chem. Soc., Perkin Trans. 1*, 1979, 3042.
8 M. M. Cambell, R. C. Craig, A. C. Hoyd, I. M. Gilbert, R. T. Logan, J. Redpath, R. G. Roy, D. S. Savage and T. Sleigh, *J. Chem. Soc., Perkin Trans. 1,* 1979, 2235.
9 K. D. Bingham, T. M. Blaiklock, R. C. B. Coleman and G. D. Meakins, *J. Chem. Soc. C*, 1970, 2330.
10 A. D. Cross, *J. Am. Chem. Soc.*, 1962, **84**, 3206.
11 K. Tori, T. Komeno and T. Nakagawa, *J. Org. Chem.*, 1964, **29**, 1136.
13 W. L. Daux, M. G. Erman, J. F. Griffin and M. E. Wolff, *Cryst. Struct. Commun.*, 1976, **5**, 775.
15 G. M. Sheldrick, SHELXS-97 Program for Crystal Structure Solution, University of Gottingen, Germany, 1997.
16 G. M. Sheldrick, SHELXL-97 Program for Crystal Structure Refinement, University of Gottingen, Germany, 1997.