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α,β-EPOXYKETONE CHEMISTRY, I:
REACTION OF HF WITH STEROIDAL 4β,5β-EPOXY-3-ONES[1]

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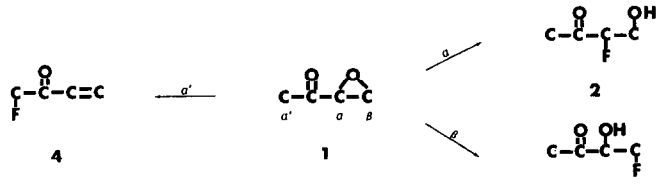
Steroidal α,β-epoxyketones serve as key intermediates in syntheses of modified hormones. The mechanistic variables, which determine the course of the reaction of α,β-epoxyketones with nucleophiles, are poorly understood. The present study is designed to explore the effects of epoxyketone structure, solvent, and nucleophile on reaction course and mechanism. The α,β-epoxyketone **1** can take three reaction paths (Scheme 1): the α-mode and the β-mode, involving trans-diaxial opening of the oxirane by nucleophile to **2** and **3**, respectively; and the α'-mode, by reaction of nucleophile at the α'-carbon, to give **4**.

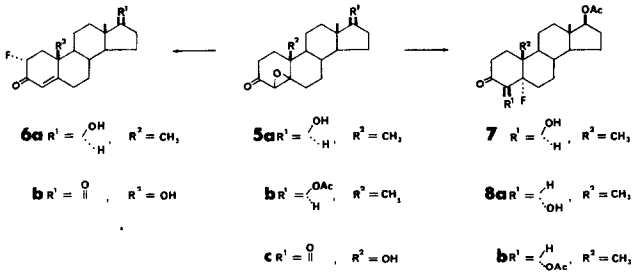


Scheme 1

Previous studies of α,β-epoxyketone reactions with HF led to conflicting results. Klimstra and Counsell[3] claimed that 17β-acetoxy-1α,2α-epoxy-5α-androstane-3-one was converted by HF in glacial HOAc to the corresponding 2-fluoro-1-en-3-one, but Kerb et al.[4] assigned to the product of HF ring opening of this epoxyketone the 4β-fluoro-1-en-3-one structure. A series of compounds synthesized by Camerino et al.[5] by reaction of steroidal 4β,5β-epoxyketones **5** with HF in $CHCl_3$/EtOH, all of which had λmax 240± 1 nm, were erroneously assigned the 4-fluoro-4-en-3-one partial structure, authentic 4-fluoro-4-en-3-ones exhibiting the chromophore 248 nm.[6]

Reaction of 4β,5β-epoxy-androstane-17β-hydroxy-3-one **5a**[5a] with HF did not occur in THF or DMF at 23°, possibly due to competition of the solvent for protons required for oxirane protonation. When 4β,5β-epoxy-androstane-17β-acetoxy-3-one **5b**[5a] was treated with HF

in neat $CHCl_3$,[7] a product (**8a**) was isolated: mp 186-189°; IR (KBr): 3462 cm^{-1} and 3510 cm^{-1} (OH), 1715 cm^{-1} (C=O); NMR ($CDCl_3$): 4.64δ (1H, q, J_{HF-aa}= 33 Hz, J_{HH}= 6.5 Hz, 4-H), 3.45δ (1H, d, J = 6.5 Hz, 4-OH), 1.13δ (3H, s, 19-CH_3); CD (dioxane): $\Delta c_{284} = -0.88$. The J_{HF} of 33 Hz indicates vicinal diaxial CH-CF[8], and hence the structure 5α-fluoro-4α,17β-dihydroxy-5α-androstane-3-one 17β-acetate **8a** was assigned to the 186-189° product.



The structure (**8a**) was confirmed by spin decoupling, which showed that the 4-OH proton doublet at 3.45δ was coupled to the 4-H proton; deuteration collapsed the 4-H signal to a doublet, and the IR ($CDCl_3$) of the deuterated product showed replacement of OH by OD bands at 2580 cm^{-1} and 2405 cm^{-1}. The splittings of 6.5 Hz in the 4-H and the 4-OH proton signals are attributed to the lack of rapid proton exchange of the 4α-OH of (**8a**), presumed to be due to intramolecular hydrogen bonding. Acetylation of the fluorohydrin (**8a**) gave the diacetate (**8b**), mp 182-184°; IR ($CHCl_3$): 1751 cm^{-1} (C=O 4-acetate), 1733 cm^{-1} (C=O 17-acetate); NMR ($CDCl_3$): 5.75δ (1H, d, J_{HF-aa} = 34 Hz, 4-H), 2.25δ (3H, s, 4-OAc), 2.05δ (3H, s, 17-OAc), 1.10δ (3H, s, 19-CH_3); CD (dioxane): $\Delta c_{302} = +0.098$, sh at 308 nm, $\Delta c_{272} = -0.088$. We interpret this reaction as regiospecific β-mode oxirane opening by fluoride to the trans-diaxial 5α,4β-fluorohydrin (**7**), followed by acid-catalyzed epimerization of the C-4 hydroxyl to give the cis-5α,4α-fluorohydrin (**8a**). A mixture of 4β,5β-epoxy-androstane-17β-ol-3-one **9** and 4α,5α-epoxy-androstane-17β-ol-3-one **5a** (β :α = 5:1 by nmr) yielded under analogous conditions, two products, isolated after acetylation in a 4:1 ratio: the major one was the diacetate (**8b**) of the 5α,4α-fluorohydrin (**8a**), and the minor product, which showed a 19-CH_3 doublet, J_{HF} = 10 Hz, and a trans-diaxial J_{HF} = 34 Hz, was assigned the structure 5β-fluoro-4β,17β-dihydroxy-5β-androstane-3-one 4,17-diacetate **10**; derived from the minor component of the starting material, the α-epoxide (**9**).

Thus both epoxides, **9** as well as **5a**, reacted with HF in neat $CHCl_3$ by the β-mode. This mode appears to be favored in situations allowing a partial positive charge to be more readily accomodated at the β- than at the α-oxirane carbon in the transition state.

The course of the α,β-epoxyketone reaction with HF is critically dependent upon solvent. When the reaction solvent was $CHCl_3$ containing 10% EtOH,[9] the product (**6a**) was isolated, mp 152-3°; UV λ max (ε): 240 (16,100); IR (KBr): 1698 cm^{-1} (conj C=O); NMR ($CDCl_3$): 5.79δ (1H, d, J = 5Hz, 4-H), 5.04δ (1H, octet, J_{HF-gem} = 49 Hz, J_{HH-ae} = 5.5 Hz, J_{HH-aa} = 13 Hz, 2-H), 1.30δ (3H, s, 19-CH_3); CD (dioxane): $\Delta\varepsilon_{335} = -2.60$; ORD (dioxane): $(\phi)_{700} = +480°$, $(\phi)_{589} = +815°$, $(\phi)_{360} = -2{,}540°$, $(\phi)_{300} = +13{,}700°$. This product was assigned the structure of 2α-fluorotestosterone **6a**.[10] Similarly, the reaction of 4β,5β-epoxy-10β-hydroxyestra-3,17-dione **5c** with HF in $CHCl_3$ / EtOH at 0° afforded 2α-fluoro-10β-hydroxy-estr-4-en-3,17-dione **6b**: mp 235-238°; UV λ max (ε): 233 (15,500); IR ($CHCl_3$): 1704 cm^{-1} (conj C=O); NMR ($CDCl_3$): 5.84δ (1H, d, J = 5 Hz, 4-H), 5.33δ (1H, octet, J_{HF-gem} = 49 Hz, J_{HH-ae} = 7 Hz, J_{HH-aa} = 14 Hz, 2-H); CD (dioxane): $\Delta\varepsilon_{344} = -1.21$, $\Delta\varepsilon_{334} = -1.32$, $\Delta\varepsilon_{316} = 0°$, $\Delta\varepsilon_{296} = +1.69$; MS: M^+, 306, fragmentation pattern consistent with proposed structure (**6b**).

The structures of the series of compounds of Camerino *et al.*,[5] all of which had λ max 240±1 nm, to which these authors had erroneously assigned the 4-fluoro-4-en-3-one structures, are now being corrected, by analogy, to the corresponding 2α-fluoro-4-en-3-one structures (**6**) arising from α'-mode ring opening. The mechanistic details of the α'-mode of oxirane are as yet unknown. Kerb *et al.*,[4] considered their reported production of 4β-fluoro-17β-hydroxy-5α-androst-1-en-3-one 17β-acetate by reaction of the corresponding 1α,2α-epoxy-3-one with HF (in THF or DMF) to be a *rearrangement* reaction, without specifying the primary product before rearrangement, while demonstrating that it could not have been 2-fluoro-17β-hydroxy-5α-androst-1-en-3-one 17β-acetate.[11] An intermediate for Kerb's postulated rearrangement does not readily present itself. We have demonstrated that β-mode oxirane opening of epoxyketone (**5a**) leads to β,α-fluorohydrin (**8a**), which if conceived as an intermediate for rearrangement, would require an unlikely 1,4-shift of fluorine to produce the α'-fluoro-α,β-en-one (**4**). We consider Kerb's "rearrangement" mechanism of an unspecified intermediate implausible. We favor a mechanism of direct fluoride reaction, in the presence of an hydroxylic solvent, at the α'-carbon of α,β-epoxyketone **1**, possibly as enol, and if so, this reaction could be viewed as a cine-substitution.

References

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3. P.D. Klimstra and R.E. Counsell, J. Med. Pharm. Chem., 5, 1216 (1962).

4. U. Kerb, G. Schulz, and R. Wiechert, Angew. Chem. internat. Edit., 7, 893 (1968).

5a. B. Camerino, B. Patelli, and A. Vercellone, J. Am. Chem. Soc., 78, 3540 (1956).

b. B. Camerino, R. Modelli, and B. Patelli, Il Farmaco Ed. Sci., 13, 52 (1958).

6a. A.H. Nathan, J.O. Babcock, and J.A. Hogg, J. Am. Chem. Soc., 82, 1436 (1960).

b. M. Neeman and Y. Osawa, Tetrahedron Letters, 1987 (1963).

7. Into ethanol-free $CHCl_3$ was pre-bubbled HF for 7 min, stopped, and the steroid added in one portion. Disappearance of starting material after 1 hr was seen by NMR. The reaction was worked up after 2 hrs.

8. J. Levisalles and M. Rudler-Chauvin, Bull. Soc. Chim. Fr., 3947 (1969).

9. HF was bubbled into $CHCl_3$ containing 10% EtOH for 10 min at 0°. A pre-cooled solution of the steroid in $CHCl_3$-EtOH was added over a period of 1 min. At the end of 3.5 min. the reaction was complete.

10. H.M. Kissman, A.M. Small, and M.J. Weiss, J. Am. Chem. Soc., 82, 2313 (1960).

11. We have also found that 4-fluoro-19-nortestosterone is stable under reaction conditions of α'-mode epoxide opening ($CHCl_3$-EtOH).