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α,β-EPOXYKETONE CHEMISTRY, II:

REACTION OF HCl AND HBr WITH STEROIDAL 4β,5β-EPOXY-3-ONES[1]

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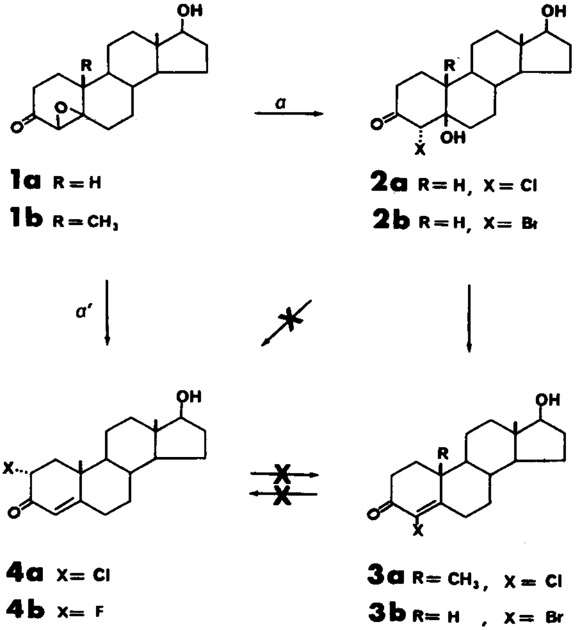
In Part I the reactions of HF with steroidal α,β-epoxyketones were shown to occur regiospecifically by two alternative modes, β or α', depending upon the solvent employed.[3] In neat $CHCl_3$, two model compounds 4β,5β-epoxy-17β-hydroxy-androstan-3-one **1b** and 4α,5α-epoxy-17β-hydroxy-androstan-3-one **5** showed β-mode regiospecificity leading to the corresponding cis-β,α-fluorohydrins. In contrast, α'-regiospecificity obtained in the reaction of the A/B cis-epoxyketone (**1b**) with HF in $CHCl_3$/EtOH, leading to the α'-fluoro-α,β-en-one (**4b**).



1a R=H
1b R=CH_3

2a R=H, X=Cl
2b R=H, X=Br

4a X=Cl
4b X=F

3a R=CH_3, X=Cl
3b R=H, X=Br

The present communication is concerned with mechanistic variables, such as ionic radii of halides, steric factors, and solvent effects, in relation to regiospecificity. To study α and α'-regiospecificities, the A/B cis-epoxyketones (**1a**) and (**1b**) were used as model compounds. In reactions with these compounds, nucleophiles having sizable steric requirements could encounter hindrance in approaching the C-5 oxirane carbon from the α-side of the molecule, an effect which would decrease the likelihood of β-mode oxirane opening by Br^- and Cl^-, in contrast to F^-, which reacts by β-mode in $CHCl_3$.[4]

Our previous finding had indicated lack of α-mode oxirane opening of F^-.[3] This conclusion was confirmed in the present study by subjecting A/B cis-epoxyketone (**1a**) to 30% aqueous HF in acetone (21°, 3 hrs), when no reaction occured. In contrast, α-mode regiospecificity was effected by reaction of epoxyketone (**1a**) in acetone solution with either 37% aqueous HCl (0°, 15 min) or 30% aqueous HBr (20°, 15 min) which afforded trans-diaxial α,β-halohydrins: 4α-chloro-5β,17β-dihydroxy-estran-3-one **2a**,[5] mp 198-200°; IR (KBr): 3480 and 3270 cm^{-1} (OH), 1735 cm^{-1} (C=O); NMR (DMSO): 4.10 δ (1H, s, 4-H), 0.67 δ (3H, s, 18-CH_3); ORD (MeOH): $(\Phi)_{700} = +127°$, $(\Phi)_{589} = +127°$, $(\Phi)_{315} = +3720°$, $(\Phi)_{294} = -3370°$; CD (MeOH): $\Delta\epsilon_{303} = +1.42$; and 4α-bromo-5β,17β-dihydroxy-estran-3-one **2b**, mp 128-129°; IR (KBr): 3487 and 3270 cm^{-1} (OH), 1714 cm^{-1} (C=O); NMR (DMSO): 4.13 δ (1H, s, 4-H), 0.68 δ (3H, s, 18-CH_3); ORD (MeOH): $(\Phi)_{700} = +260°$, $(\Phi)_{589} = +260°$, $(\Phi)_{332} = +5600°$, $(\Phi)_{287} = -8860°$, $(\Phi)_{278} = -9300°$; CD (dioxane): $\Delta\epsilon_{308} = +3.52$, sh at 300 and 313 nm. The α,β-bromohydrin (**2b**) was converted to 4-bromo-17β-hydroxy-estr-4-en-3-one **3b**[6] in the same reaction medium (30% HBr in acetone) at higher temperature (57°, 1 hr). The α-mode reaction capabilities of Cl^- and Br^-, as contrasted to the lack of such capability of F^-, reflect the greater polarizabilities of the larger X^-; conceivably some degree of orbital overlap with carbonyl in the transition state is involved in α-mode oxirane opening.

The propensity of α-mode reactivity of Cl^- suggested that under conditions leading to α'-mode regiospecificity of F^-, the corresponding reaction of Cl^- would not be α'-regiospecific. Indeed, when epoxyketone (**1b**) was subjected to reaction with HCl in $CHCl_3$/EtOH,[7] two products were isolated in a 1:1 ratio: product A, UV (EtOH): 256 (14,700) was identified as 4-chlorotestosterone **3a**,[8] and product B, UV (EtOH): 243 (14,800); NMR ($CDCl_3$): 5.90 δ (1H, s, 4-H), 4.70 δ (1H, q, J_{ae} = 5.5 Hz, J_{aa} = 14 Hz, 2-H) was 2α-chlorotestosterone **4a**,[9] indicating a 1:1 ratio of α:α'-mode oxirane opening. This α:α' ratio could be altered by changes in reaction conditions: when the solvent was THF,[10a] the ratio α:α' was 2:1; when the HCl/THF ratio was decreased,[10b] α-mode regiospecificity was attained, with concomitant reduction in reaction rate. The reported product ratios of **3a**:**4a** can be viewed as reflecting α:α'-mode ratios, assuming no chloride migration in conversion of primary to final reaction products. The following experiments support this assumption: (i) a 1:1 mixture of **3a**:**4a**, when exposed to THF/HCl,[10a] was recovered unchanged, indicating no α'→α migration of Cl; (ii) when (**3a**) was exposed to HCl in $CHCl_3$/EtOH,[7] it was recovered unchanged, indicating no α→α' migration; (iii) when (**2a**) was exposed to HCl in $CHCl_3$/EtOH,[7] 4-chloro-17β-hydroxy-estr-4-en-3-one **3c**[11] was obtained, and no products containing a 2-chloro-substituent were formed, ruling out a 4α,5β-chlorohydrin as an intermediate in α'-mode reaction leading from epoxyketone (**1b**) to 2α-chlorotestosterone **4a**. These findings enlarge the scope of the α'-mode reaction of α,β-epoxyketones to encompass nucleophilic cine-chlorination in addition to cine-fluorination.

References

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2. Supported by a NIH Traineeship from NIH-PHS Institutional Training Grant CA-5016-14, 1969-1970, and by a New York State Fellowship, 1970-1971. Abstracted, in part, from the doctoral dissertation of J.S. O'Grodnick, in partial fulfillment of requirements for the Ph.D. degree.

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4. The lack of evidence for the operation of steric approach control in the β-mode oxirane opening by HF in CHCl$_3$ (β-regiospecific reactions of both the A/B *trans*-epoxyketone **5** and the A/B *cis*-epoxyketone **1b**) is interpreted as a reflection of the small steric requirement of F$^-$ in CHCl$_3$.

5. All new compounds had satisfactory analytical data.

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7. HCl was bubbled into CHCl$_3$ containing 10% EtOH for 7 min, and the steroid added in one portion. After 3 min at 23° the reaction mixture was worked up.

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(b). H.J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, *21*, 1432 (1956).

9. K. Yasuda, *Chem. Pharm. Bull.* (Japan), *12*, 1217 (1964).

10(a). Into THF at 0° was bubbled anhydrous HCl for 10 min, and the epoxyketone (**1b**) in THF at 0° was added in one portion.

(b). Dilution of reaction mixture (a) with THF prior to addition of epoxyketone (**1b**), in a 1:10 ratio, gave 4-chlorotestosterone **3a** in 30% yield, with recovery of epoxyketone (**1b**) in 70% yield. Higher dilution (1:100 and 1:1000) precluded reaction.

11. Y. Nomura, B. Takegawa, and I. Chumu, Japan. Pat. 8232 (1960).