Neighbouring Hydroxy-group Participation in the Opening of Epoxides by Nucleophiles

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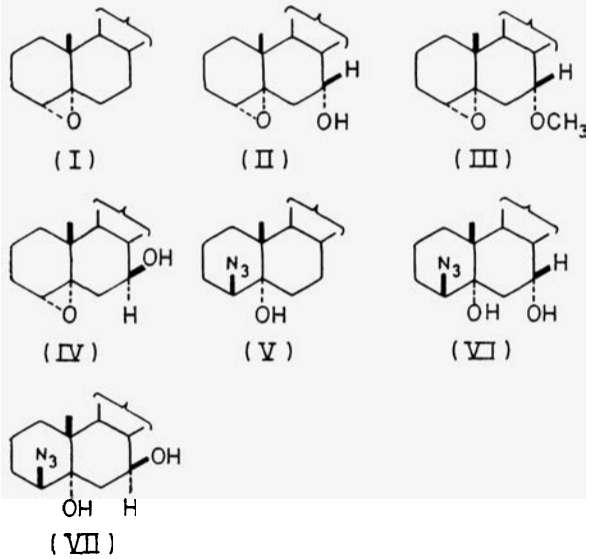
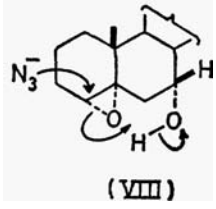
Summary 4α,5α-Epoxycholestane and some of its derivatives were prepared and their reactions with sodium azide in refluxing acetone–water were studied; the presence of a 7α-hydroxy-group in the steroidal skeleton accelerates the opening of the epoxy ring by the nucleophile.

IN our previous study[1] on the base-catalysed opening of steroidal β,γ-epoxy-ketones into the corresponding γ-hydroxy-α,β-unsaturated ketones, no neighbouring hydroxy-group participation had been observed. We expected that the neighbouring hydroxy-group would accelerate the



process by delocalization of the negative charge developing on the epoxide oxygen during the opening of the ring. However, it was found[1] that in these systems the rate determining step is the enolization and not the ring opening and this was the reason why no anchimeric assistance could be detected.

In our present work we investigated the effect of a neighbouring hydroxy-group on the opening of epoxides by nucleophiles. In such a bimolecular process, the cleavage of the epoxide ring takes place in the rate determining step.[2] For this purpose 4α,5α-epoxycholestane (I) and its derivatives (II—IV) were prepared and their reactions with azide anions as the nucleophile were studied.



4α,5α-Epoxycholestane (I),[3] m.p. 101—102°, $[\alpha]_D$ + 71 ($CHCl_3$), was obtained by epoxidation of cholest-5-ene. 4α,5α-Epoxy-7α-hydroxycholestane (II), m.p. 107—109°, $[\alpha]_D$ + 38 ($CHCl_3$) was prepared either by epoxidation of ψ-cholesterol or by reduction of 4α,5α-epoxycholestan-7-one. 4α,5α-Epoxy-7α-methoxycholestane (III), m.p. 64—66°, $[\alpha]_D$ + 48 ($CHCl_3$) was obtained by methylation of (II). 4α,5α-Epoxy-7β-hydroxycholestane (IV), m.p. 60—62°, $[\alpha]_D$ + 91 ($CHCl_3$), was obtained by epoxidation of 7β-acetoxycholest-4-ene and then hydrolysis of the acetate group.

Treatment of each of (I—IV) in acetone–water (2:1) under reflux with a 100-fold excess of sodium azide gave the corresponding azides: (V) from (I), m.p. 127—128° $[\alpha]_D$ + 74° ($CHCl_3$), (VI) from (II), m.p. 216—218° $[\alpha]_D$ + 48° ($CHCl_3$), (VII) from (IV), m.p. 239—241°, $[\alpha]_D$ + 85 ($CHCl_3$).

We estimated half-lives for the above pseudo-first-order reaction: 5 ± 1, 90 ± 10 and 450 ± 50 h for (II), (IV), and (I) respectively. The 7α-methoxyepoxide (III) does not react under these conditions and can be recovered even after 500 h.

There is a significant rate enhancement in (II) compared to (I), (III), and (IV), and we believe that this results from

an intramolecular electrophilic neighbouring group assistance, since only in (II) is the neighbouring 7α-hydroxy-group in a position which enables negative charge delocalization in the transition state (VIII).

The above reaction with azide anion as well as reactions with other nucleophiles and their detailed mechanism are now being investigated. All substrates as well as products have satisfactory analyses and stereochemical structure proof.

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[3] R. E. Ireland, T. I. Wrigley, and W. G. Young, *J. Amer. Chem. Soc.*, 1958, **80**, 4604.