The Acid-catalysed Ring-opening of Epoxides in a Largely Nonaqueous Medium

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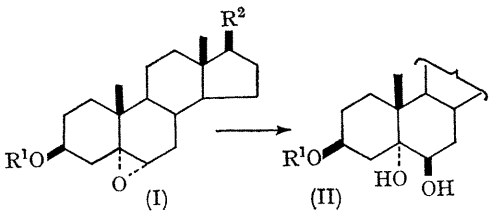
Summary In the slow stage of the acid-catalysed ring-opening of steroidal 5,6-epoxides in ethyl methyl ketone containing a little water, breaking of the O–C-6 bond is thought to be appreciably advanced before the protonated epoxide is attacked by the incoming nucleophile.

ALTHOUGH the acid-catalysed hydrolysis of epoxides to glycols has been widely investigated,[1] there appears to be no information about the kinetics in largely non-aqueous media. The study of such a system (see Scheme) reveals points of mechanistic and preparative interest.

Steroid substrates were chosen in order that stereochemical features could be discerned, and the reactions followed conveniently with a recording polarimeter ($\Delta[\alpha]_D$ *ca.* 60° at 436 nm.) Ethyl methyl ketone was selected as a solvent in which the proportions of reactants could be varied widely, and perchloric acid as the catalyst since it is completely ionised in media containing appreciable amounts of water. The products, formed in quantitative yield, were shown to be 5α,6β-diols: the hydrolyses are thus clean *trans*-diaxial ring-openings, free of complications such as backbone rearrangements.[2]

The reactions are first order with respect to epoxide, but more complex in their dependence on perchloric acid and water. (See values of p and q.) While no single mechanism appears to accommodate all the details, the sequence shown (which is based on a model suggested by Parker and Isaacs[1]) gives a satisfactory qualitative explanation. Hydronium ion is considered to be the protonating agent; with the perchloric acid: water ratios used it is rather unlikely that the ketone solvent is protonated to an appreciable extent. In the transition state of the slow stage, breaking of the O–C-6 bond is thought to be more advanced than bond-making: a partial positive charge develops at C-6 while the incoming water molecule is still relatively far away. Such a borderline mechanism would explain the absence of acceleration by added water (characteristic of an $A1$ cleavage) and the observed stereochemical result (suggestive of an $A2$ reaction). The variation in acid dependence (p) of the rate is taken to mean that, at higher acid concentrations, the epoxide is attacked by perchloric acid in the form of ion pairs. (An alternative explanation, based on protonation by the conjugate acid of the solvent ketone, is not excluded.)

SCHEME

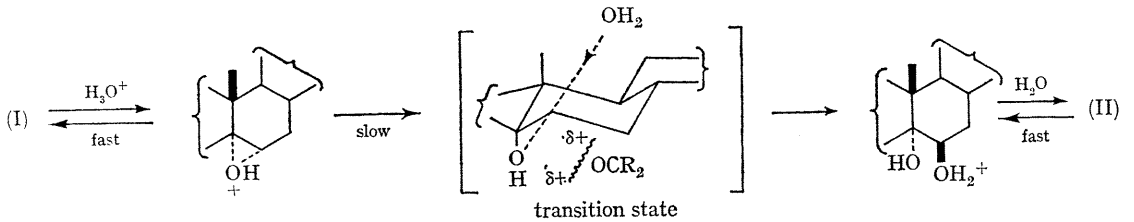


a; R^1 = OMe; R^2 = H
b; R^1 = 3,5-$(NO_2)_2C_6H_3$·CO; R^2 = H
c; R^1 = 3,5-$(NO_2)_2C_6H_3$·CO; R^2 = C_8H_{17}

Epoxide (I) (1 mol., 40 mg.), $HClO_4$ [x(0·01—5) mol.], H_2O[y(5—120) mol.] in Et·CO·Me (7 ml.)

$$d[II]/dt = k_1[I] \text{ where } k_1 = \text{const. } [HClO_4]^p/[H_2O]^q$$

(i) $k_1 = 2 \times 10^{-2}$—$1{\cdot}5 \times 10^{-6}$ at 20°, (ii) $p = 1$ at $x = ca.$ 0·1, $p = 2$ at $x = ca.$ 3 [*e.g.*, For $y = 25$, $p = ca.$ 1·5 at $x = 1$ for (Ib, c), and at $x =$ 0·6 for (Ia)], (iii) $q = 1{\cdot}6$—2·4, (iv) k_1 not influenced by added $NaClO_4$, (v) k_1 for (Ia) = *ca.* twice k_1 for (Ib, c) under comparable conditions, (vi) $E_a = ca.$ 20 kcal. mole^{-1}, and $\Delta S^{\ddagger} = ca.$ — 37 cal. deg.$^{-1}$ mole^{-1} in the range 15—55°.



Inhibition of the reaction by added water follows from a lowered concentration of the protonated epoxide formed in the fast, reversible first stage, but it is difficult to attach significance to the precise values of q. Many procedures for hydrolysing steroid epoxides involve long reaction times or elevated temperatures.[3] Our observation that the reactions are rapid at *low* water concentration led to the following method: epoxide (Ib, 250 mg.) in dry ethyl methyl ketone (18 ml.) containing perchloric acid (0·09 ml. of 60% reagent) was hydrolysed to the triol-monoester (IIb, 95%) within 5 min. at 20°.

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[1] R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 1959, **59**, 737.
[2] D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, Amsterdam, 1968, p. 353 *et seq.*
[3] C. Djerassi, "Steroid Reactions," Holden-Day, San Francisco, 1963, p. 626 *et seq.*