MECHANISM OF ACID CLEAVAGE OF SOME STEROID EPOXIDES. COMPETITION BETWEEN NEIGHBORING GROUP PARTICIPATION AND EXTERNAL NUCLEOPHILE ATTACK

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The mechanism of perchloric acid cleavage of epoxides *I* and *II* was established on the basis of experiments using $H_2{}^{18}O$. The 2α,3α-epoxide *I* gave two products: the cyclic ether *V* (60%) arising by $5(O)^n$ participation of the 19-acetoxyl and the diol *VI* (40%). The latter compound is formed by two mechanisms: *1*) By direct cleavage of the oxirane ring with $H_2{}^{18}O$ as external nucleophile and *2*) by $7(O)^{\pi,n}$ participation *via* the ion *III*. Under the same conditions the 5α,6α-epoxide *II* yielded two diols: The diequatorial diol *VIII* (96%) arising by $6(O)^{\pi,n}$ participation and the diaxial diol *IX* which is again formed by both direct cleavage of the oxirane ring with $H_2{}^{18}O$ and by $7(O)^{\pi,n}$ participation *via* the intermediate ion *X*. The competition of several mechanisms is discussed.

In earlier papers[1,2] we reported cleavage of 2α,3α- and 5α,6α-epoxides *I* and *II* bearing an acetoxy group at position 19. On treatment with aqueous perchloric acid in dioxane the 2α,3α-epoxide *I* yields two products: the cyclic ether *V* (60%) and the diaxial diol *VI* (40%). Cleavage of the 5α,6α-epoxide *II* gives the diequatorial diol *VIII* (96%) as the major product, the minor product being its diaxial isomer *IX* (4%).

Formation of the cyclic ether *V* from the 2α,3α-epoxide *I* is due to $5(O)^n$ participation of the 19-acetoxy group[1]. The diaxial diol *VI*, however, may arise by two routes, either on cleavage of the oxirane ring by water acting as an external nucleophile, or by $7(O)^{\pi,n}$ participation of the acetoxy group *via* an intermediate cyclic ion *III* hydration of which would eventually give the diol *VI*. The earlier[1] work was based on product analysis which did not permit to decide which alternative is operative. The anomalous cleavage of the 5α,6α-epoxide *II* yielding the diequatorial diol *VIII* was rationalized[1,2] by $6(O)^{\pi,n}$ participation (for notation *cf.* ref.[3]) of the 19-acetoxy group and this view was supported by assuming an analogy with the behavior of the corresponding 19-ethoxycarbonyl derivative where the participation was clearly

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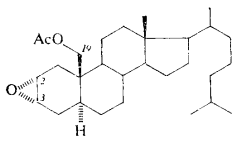
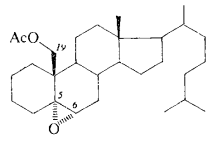
demonstrated[1]. The minor product *IX* can arise by two routes, either *a*) by a direct reaction of the oxirane ring with water acting as an external nucleophile or *b*) by $7(O)^{\pi,n}$ participation of the 19-acetoxy group *via* the cyclic ion *X*.

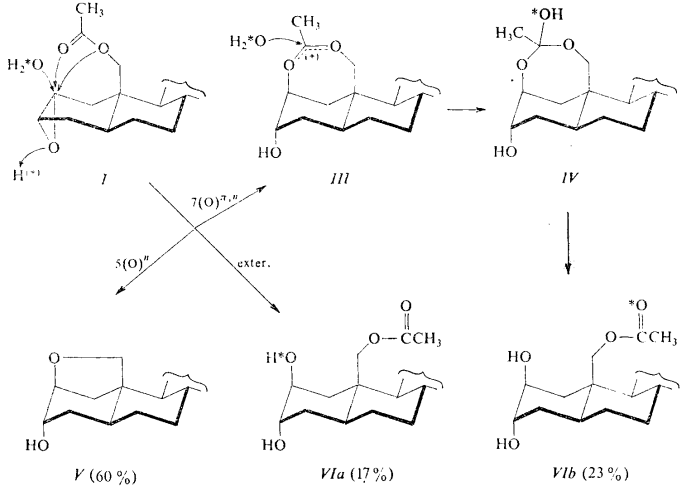


I



II

We now present direct proof for the mechanism of formation of the diols *VI*, *VIII* and *IX* based on experiments carried out in the presence of water enriched in ^{18}O isotope. If the diol is formed on direct cleavage of the epoxide by water as an external nucleophile, all ^{18}O incorporated into the steroid molecule must be present in the hydroxyl group. On the other hand, if the diol formation involves $6(O)^{\pi,n}$ or $7(O)^{\pi,n}$ participation by the carbonyl oxygen of the acetoxy group (*via* the corresponding

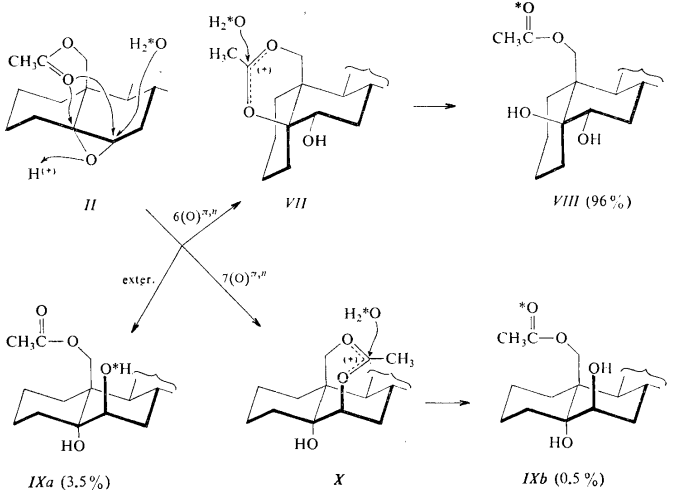


SCHEME 1

cyclic ion), the ^{18}O must be incorporated into the carbonyl of the acetoxy group.

The 2α,3α-epoxide *I*, on treatment with perchloric acid in dioxane containing water enriched in $H_2{}^{18}O$ (27%), is cleaved in the following manner (Scheme 1): $5(O)^n$ participation yields the cyclic ether *V* as the major product. The minor product, the diaxial diol *VI*, contains the ^{18}O isotope both in the 2β-hydroxyl (*VIa*, 42%) and in the acetoxy group (*VIb*, 58%) as demonstrated by mass spectrometry (Tables I and II). Formation of the diol *VI* is thus due to both mechanisms, *i.e. a*) to direct cleavage of the oxirane ring by water as an external nucleophile (*I*→*VIa*) and *b*) to $7(O)^{\pi,n}$ participation of the 19-acetoxy group *via* the cyclic ion *III*, its hydration to the intermediate *IV* eventually providing the diol *VIb*.

Under the same conditions, the 5α,6α-epoxide *II* gives the diequatorial diol *VIII* as the major product. Since this diol contains practically all the ^{18}O isotope in the acetoxy group (>95%), it must be exclusively formed by fission of the oxirane ring at $C_{(5)}$ by the carbonyl oxygen of the 19-acetoxy group, *i.e.* by $6(O)^{\pi,n}$ participation (*II*→*VII*→*VIII*) as shown in Scheme 2. The minor product, the diaxial diol *IX*, contains the ^{18}O isotope predominantly in the hydroxyl group (*IXa*, 88%), while the acetoxy group contains the remaining 12% of the oxygen isotope ^{18}O (*IXb*). It fol-



SCHEME 2

lows from these facts that most of the diol *IX* is formed by cleavage of the oxirane ring by water as an external nucleophile (*II*→*IXa*). The competitive fission by $7(O)^{\pi,n}$ participation (*II*→*X*→*IXb*) contributes to its formation only to a limited extent.

TABLE I

The content of ^{18}O in the products of the cleavage of the epoxides *I* and *II*

Compound	Ion	Content of ^{18}O, %
VI	$M^{+\cdot}$	21·2 ± 0·7
	$(M-H_2O)^{+\cdot}$	15·8 ± 0·7
	$(M-2\,H_2O)^{+\cdot}$	16·1 ± 0·4
	$(M-CH_3CO_2H)^{+\cdot}$	11·7 ± 0·4
	$(M-CH_3CO_2H-H_2O)^{+\cdot}$	4·7 ± 0·2
VIII	$M^{+\cdot}$	22·9 ± 0·5
	$(M-H_2O)^{+\cdot}$	22·7 ± 0·7
	$(M-2\,H_2O)^{+\cdot}$	17·3 ± 0·7
	$(M-H_2O-CH_3)^{+}$	22·0 ± 0·7
	$(M-CH_3CO_2H)^{+\cdot}$	0·5 ± 0·2
	$(M-CH_3CO_2H-H_2O)^{+\cdot}$	0·0 ± 0·2
IX	$(M-H_2O)^{+\cdot}$	3·3 ± 0·4[a]
	$(M-CH_3CO_2H)^{+\cdot}$	24·5 ± 0·3
	$(M-CH_3CO_2H-H_2O)^{+\cdot}$	18·3 ± 0·0[a]
	$(M-CH_3CO_2H-CH_2OH)^{+}$	17·3 ± 0·1

[a] Different mechanisms of water elimination.

TABLE II

Corrected distribution of ^{18}O in the diols *VI*, *VIII* and *IX*

Compound	Position of the label	Content of ^{18}O, %[a]
VI	19-O_2CCH_3	58
	2β-OH	42
VIII	19-O_2CCH_3	>95
	5β-OH	< 5
IX	19-O_2CCH_3	12
	6β-OH	88

[a] Corrected for 100%-content of ^{18}O.

Blank experiments were carried out by treatment of the unlabeled diols *VI*, *VIII* and *IX* for 3 h in a reaction medium identical with that used for the cleavage of epoxides. Practically no ^{18}O was incorporated into the acetoxy group.

In the case of 2α,3α-epoxide *I*, the $6(O)^{\pi,n}$ participation is not possible. Even so, participation processes predominate, the $5(O)^n$ participation being the major, the $7(O)^{\pi,n}$ the minor reaction. External attack by water occurs to about the same extent as the $7(O)^{\pi,n}$ participation. With the 5α,6α-epoxide *II*, the $6(O)^{\pi,n}$ participation largely predominates; $5(O)^n$ participation, though formally possible, is not operative[1].

The 2α,3α- and 5α,6α-epoxides *I* and *II* are not equally prone to $7(O)^{\pi,n}$ participation. The 2α,3α-isomer *I* shows a greater tendency to undergo this reaction than its 5α,6α-counterpart *II*. All these results are in line with those obtained in hypobromous acid addition to the corresponding 2,3- and 5,6-unsaturated derivatives (*cf.* previous paper[6]). Generally, as follows from the investigations presented here and in the previous papers[1–6], the bromonium ions are more prone to neighboring group participation than are the corresponding epoxides. Moreover, similar to the previous paper[6], these results bring evidence for the existence of the cyclic seven-membered acetoxonium ion as intermediate.

EXPERIMENTAL

The identity of the labeled compounds was checked by TLC, by their ^{1}H-NMR (recorded on a Tesla B 476 instrument in deuteriochloroform with tetramethylsilane as internal reference) and mass spectra (measured on a JEOL JMS D-100 apparatus at 75 eV) and by comparison of the R_F values and the spectra with those of the unlabeled compounds prepared earlier[1]. The ^{18}O-content (Table I) of the compounds was determined by mass spectrometry. The samples were introduced using a direct inlet heated to 120–150°C, the ion source being maintained at 150°C. The intensities of ion species were recorded at a constant total ion current and scan rate of 60 min/mass decade. The intensity values were averaged over at least four scans and then corrected for natural abundance[7] of ^{13}C, ^2H and ^{18}O isotopes. The correcting factors were taken from the mass spectra of the corresponding unlabeled compounds.

Cleavage of the Epoxides *I* and *II*

The epoxide (200 mg) was dissolved in dioxane (5 ml) and treated with a solution (1 ml) prepared from a solution of 27% $H_2{}^{18}O$ in $H_2{}^{16}O$ (1·6 ml), dioxane (6·2 ml) and 72% aqueous perchloric acid (0·2 ml) at room temperature for 1 h. The product was precipitated with water, extracted with ether and the ethereal layer was washed with water, a 5% aqueous potassium hydrogen carbonate solution, and water, dried and evaporated. The residue was chromatographed on four silica gel plates with a mixture of light petroleum, ether and acetone (80 : 10 : 10) as given[1] for unlabeled compounds.

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