# PARTICIPATION OF 19-SUBSTITUENTS IN ACID CLEAVAGE OF STEROIDAL 5α,6α-EPOXIDES

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Participation of the 19-methoxy and 19-acetoxy group in 5α,6α-epoxides *IIIa* and *IVa* on treatment with aqueous perchloric acid or hydrobromic acid is investigated and compared with acid cleavage of previously studied 3β-acetoxy epoxides *IIIb* and *IVb*. The methoxy group in *IIIa* participates by a $5(O)^n$ process. The participation is predominant on treatment with perchloric acid but is completely suppressed by the attack of an external nucleophile on treatment with hydrobromic acid. The acetoxy group in *IVa* participates by a $6(O)^{\pi,n}$ process. Participation is predominant on treatment with perchloric and is only partially suppressed by a competitive external nucleophile attack on the action of hydrobromic acid. This behavior constitutes a difference to the 3β-acetoxy derivative *IVb* where hydrobromic acid completely suppresses the participation in favor of an external attack.

On cleavage by a nucleophilic species, the protonated epoxide ring reacts similarly to the bromonium ion[1-3]. As we have demonstrated on reactions of steroid model compounds this analogy is particularly obvious when the position and steric location of both compared groups is identical[4-6]. Recently, we investigated the participation of 19-substituents in the course of hypobromous acid addition to 5,6-unsaturated steroids[7-9]; we were particularly concerned with the influence of the 3β-acetoxy groups on these reactions[10]. It is of interest to compare these results with the behavior of 6α,7α-epoxides under the influence of strong acids representing a weak (aqueous perchloric acid) and strong (hydrobromic acid) type of nucleophile.

The compounds used for the experiments were 19-methoxy and 19-acetoxy 5α,6α-epoxides *IIIa* and *IVa* prepared[11] from olefins *Ia* and *IIa*. These compounds are representatives of two different types: The methoxy group can participate only in $(O)^n$ processes, whereas the ambident acetoxy group can take part in both $(O)^n$ and $(O)^{\pi,n}$ participations (for notation ref.[9]).

When the 19-methoxy derivative *IIIa* was treated with aqueous perchloric acid, the main product of the reaction was the cyclic ether *Va*; minor products were the diol *VIa* and the allylic alcohol *IX* (Table I). Treatment of *IIIa* with hydrobromic acid in aqueous dioxane yielded solely the bromohydrin *VIIa*.

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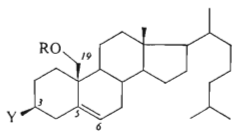
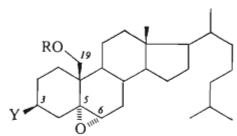
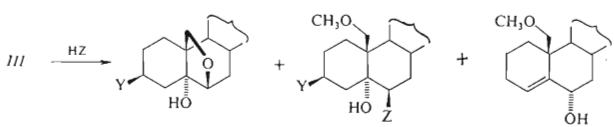
When the 19-acetoxy derivative *IVa* was treated with aqueous perchloric acid, the resulting reaction mixture consisted predominantly of the diequatorial diol *Xa* which was accompanied by the diaxial diol *XIIa*. Treatment of *IVa* with aqueous hydro-



*Ia*, R = $CH_3$, Y = H
*Ib*, R = $CH_3$, Y = AcO
*IIa*, R = Ac, Y = H
*IIb*, R = Ac, Y = AcO



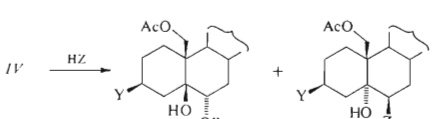
*IIIa*, R = $CH_3$, Y = H
*IIIb*, R = $CH_3$, Y = AcO
*IVa*, R = Ac, Y = H
*IVb*, R = Ac, Y = AcO



*Va*, Y = H
*Vb*, Y = AcO

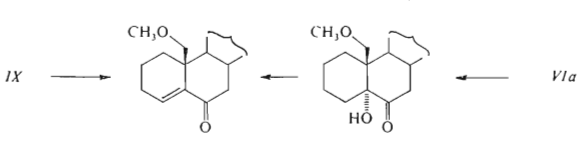
*VIa*, Z = OH, Y = H
*VIb*, Z = OH, Y = AcO
*VIIa*, Z = Br, Y = H
*VIIb*, Z = Br, Y = AcO
*VIII*, Z = $ONO_2$, Y = H

*IX*



*Xa*, R = H, Y = H
*Xb*, R = H, Y = AcO
*XI*, R = Ac, Y = H

*XIIa*, Z = OH, Y = H
*XIIb*, Z = OH, Y = AcO
*XIIIa*, Z = Br, Y = H
*XIIIb*, Z = Br, Y = AcO
*XIV*, Z = OAc, Y = H



*XV* *XVI*

bromic acid yielded in about 1 : 1 ratio the diol *Xa* and the bromohydrin *XIIIa* (Table I).

Structures of the reaction products were proved in the following manner. The structure of the cyclic ether *Va* is based mainly on spectral evidence. In the $^1$H-NMR spectrum the signal of the methoxy group is absent while the narrow multiplet associated with the $C_{(6)}$—H is indicative of axial conformation of the $C_{(6)}$-oxygen atom. The IR spectrum discloses the presence of a free tertiary hydroxy group. The structure *Va* is also in agreement with mass determination and elemental analysis. The diol *VIa* and its nitrate *VIII* were identified with compounds described earlier[11]. The bromohydrin *VIIa* cyclizes readily to the parent epoxide *IIIa* which indicates the diaxial arrangement of the OH and Br groups. The $^1$H-NMR spectrum of *VIIa* shows the presence of the 19-methoxyl and the width of the $C_{(6)}$-H multiplet confirms the 6β-configuration of the bromine atom. The structure of the allylic alcohol *IX* was derived from spectral and chemical evidence: The position of the hydroxy group and double bond was proved by correlation with the diol *VIa*. The latter was oxidized with pyridinium chlorochromate[12] to the hydroxy ketone *XVI* which was dehydrated by treatment with thionyl chloride to yield the α,β-unsaturated ketone *XV* dentical with the compound prepared by oxidation of *IX*.

For the structure of the diols *Xa* and *XIIa* the data obtained from the IR and $^1$H-NMR spectroscopy proved the presence of the 19-acetoxy group but were not

TABLE I

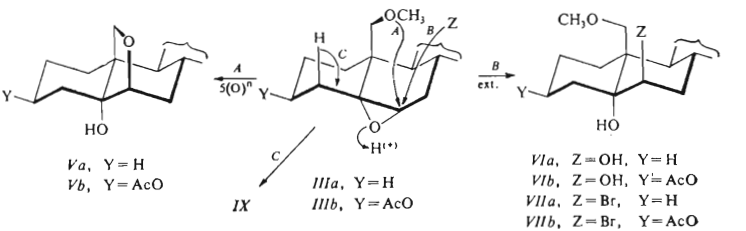
Yields and Ratios of Epoxides *III* and *IV* Cleavage Products

| Starting compound | Neighboring group | Reagent | Mode of reaction, % of the total yield | | | Total yield % | Ref. |
|---|---|---|---|---|---|---|---|
| | | | 5(O)$^n$ | 6(O)$^{n-n}$ | Ext.[a] | | |
| *IIIa* | $OCH_3$ | $HClO_4$ | 18 (*Va*) | — | 63 (*VIa*) | 98[b] | — |
| *IIIa* | $OCH_3$ | HBr | — | — | 100 (*VIIa*) | 95 | — |
| *IIIb* | $OCH_3$ | $HClO_4$ | 27 (*Vb*) | — | 73 (*VIb*) | 87 | 4 |
| *IIIb* | $OCH_3$ | HBr | — | — | 100 (*VIIb*) | 94 | 4 |
| *IVa* | OAc | $HClO_4$ | — | 96 (*Xa*) | 4 (*XIIa*) | 87 | — |
| *IVa* | OAc | HBr | — | 49 (*Xa*) | 51 (*XIIIa*) | 98 | — |
| *IVb* | OAc | $HClO_4$ | — | 97 (*Xb*) | 3 (*XIIb*) | 88 | 13 |
| *IVb* | OAc | HBr | — | — | 100 (*XIIIb*) | 92 | 5 |

[a] Product of attack of external nucleophile; [b] also 19% of *IX*.

fully informative of the remaining structural features. Therefore, both diols were acetylated to yield the diacetoxy derivatives *XI* and *XIV*. Only *XI* has an intramolecular hydrogen bridge; the configurations of 6-acetoxy groups in *XI* and *XIV* follow from the width of the multiplets corresponding to the protons at $C_{(6)}$ in the $^1$H-NMR spectrum. The bromohydrin *XIIIa* cyclizes readily to the epoxide *IVa*. From its $^1$H-NMR spectrum follows the presence of the 19-acetoxy group and β-configuration of the 6-bromine atom.

The routes leading to products obtained from the methoxy epoxide *IIIa* are represented in Scheme 1. On treatment with perchloric acid, the 5(O)$^n$ participation

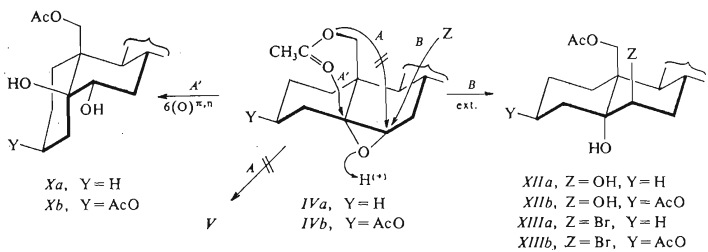



SCHEME 1

leading to the cyclic ether *Va* predominates (path *A*), but competing external attack by water is also operative (path *B*). The path *C* involves elimination of the 4β-proton and leads to the allylic alcohol *IX*. Both routes *A* and *C* are completely suppressed on hydrobromic acid treatment (Table I). Exclusive operation of external attack (under formation of the bromohydrin *VIIa*) is characteristic behavior of the strongly nucleophilic bromine ion that was shown[4-6] to suppress neighboring group participation in favor of external attack. The 3β-acetoxy derivative *IIIb* reacts similarly with perchloric acid[4] the only difference being that the pathway *C* is not operative presumably due to the inductive effect of the 3β-acetoxy group. Similarly as in the 3-unsubstituted series, treatment of *IIIb* with hydrobromic acid leads solely[4] to the bromohydrin *VIIb*.

The variety of reaction pathways considered for the 19-acetoxy 5α,6α-epoxides *IVa* and *IVb* is shown in Scheme 2. Only two pathways were actually found. Pathway *A'* represents the 6(O)$^{n,n}$ participation and pathway *B* depicts the attack by an external nucleophile. The 5(O)$^n$ participation (path *A*) is not operative at all. Action of aqueous perchloric acid on the 3-unsubstituted epoxide *IVa* leads largely to the product of 6(O)$^{n,n}$ participation, the diequatorial diol *Xa* (Table I). The 3β-acetoxy epoxide *IVb* and its 3β-fluoro analog were reported by other authors[13,14] to react similarly.

Alternative attack of water as external nucleophile at $C_{(5)}$ which would lead again to *Xa* may be excluded on the bais of our earlier results in 3β-substituted series[5].




*Xa*, Y = H
*Xb*, Y = AcO

*IVa*, Y = H
*IVb*, Y = AcO

*XIIa*, Z = OH, Y = H
*XIIb*, Z = OH, Y = AcO
*XIIIa*, Z = Br, Y = H
*XIIIb*, Z = Br, Y = AcO

SCHEME 2

The action of hydrobromic acid on the epoxide *IVa* gives products of both reaction pathways (*A'* and *B*) in approximately equal amounts (Table I). When compared with perchloric acid cleavage, the change in ratio of products in favor of the product of external attack is in accord with our previous observation that external attack by a strong nucleophile can suppress neighboring group participation[4-6]. Comparison with hydrobromic acid cleavage of the 3-substituted epoxide *IVb* shows a pronounced shift in favor of the external attack in epoxide *IVb* where the neighboring group participation is completely suppressed[5] (Table I). This fact should be attributed to electron withdrawing effect of the 3β-acetoxy group[15-21] which may suppress the cleavage of the epoxide ring at $C_{(5)}$ (ref.[1,2,22-26]) and is in line with similar observation in hypobromous acid addition to the 5,6-double bond[9,10].

It is of interest to compare the extent of suppression of the $5(O)^n$ participation (operative in 19-methoxy epoxides *IIIa*, *IIIb*) with the suppression of $6(O)^{\pi,n}$ participation (operative in 19-acetoxy epoxides *IVa*, *IVb*) in favor of external attack by strong nucleophiles. On the action of hydrobromic acid, suppression of $5(O)^n$ participation is complete whereas it is only partial for $6(O)^{\pi,n}$ participation. This finding is presumably related to our earlier observation that the $6(O)^{\pi,n}$ participation takes precedence over the $5(O)^n$ process[6,8,9].

## EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/26 Pa (0·2 Torr). Optical measurements were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane unless otherwise stated. The $^1$H-NMR spectra were recorded on a Tesla BS 476 instrument (60 MHz)

in deuteriochloroform at 30°C with tetramethylsilane as internal reference. Chemical shifts are given in ppm. Apparent coupling constants were obtained from the first order analysis. The CD spectra were recorded on a Dichrographe II (Jouan–Roussel) in dioxane. The mass spectra were recorded on a Jeol JMS D—100 spectrometer operating at 14—75 eV. The samples were introduced using a direct inlet at lowest temperature enabling evaporation. The elemental compositions of ions were determined by accurate mass measurement. The identity of the samples prepared by different routes was checked by mixture melting point determination, by thin-layer

TABLE II

$^1$H-NMR Data of the Products of Epoxide Cleavage

| Compound | 18-H | 19-H[a] | 6-H ($W$ or $J$ in Hz) |
|---|---|---|---|
| *Va* | 0·70 | 3·81 | 3·66 m (10) |
| *VIa* | 0·66 | 3·67 | 3·40 m[b] |
| *VIIa* | 0·72 | 3·81 | 3·95 m[b] |
| *IX* | 0·68 | 3·42 | 4·25 m (30) |
| *Xa* | 0·63 | 4·25 | 3·90 dd ($J_{6\beta,7\beta}$ = 5, $J_{6\beta,7\alpha}$ = 11) |
| *XIIa* | 0·65 | 4·55 | 3·48 m (12) |
| *XIIIa* | 0·68 | 4·65 | 3·97 m (*12*) |

[a] Center of an AB system; [b] overlapped by other signals.

TABLE III

Analytical and Physical Data of Epoxide Cleavage Products

| Compound | Formula (m.w.) | Calculated/Found | | M.p., °C $[\alpha]_D^{20}$ |
|---|---|---|---|---|
| | | % C | % H | |
| *Va* | $C_{27}H_{46}O_2$ (402·7) | 80·54 80·44 | 11·51 11·57 | 125—126 + 8° |
| *IX* | $C_{28}H_{48}O_2$ (416·7) | 80·71 80·65 | 11·61 11·69 | 106—108 +72° |
| *Xa* | $C_{29}H_{50}O_4$ (462·7) | 75·28 75·03 | 10·89 10·91 | foam +28° |
| *XIIa* | $C_{29}H_{50}O_4$ (462·7) | 75·28 75·11 | 10·89 10·93 | foam — 4° |

chromatography (TLC) and by infrared and $^1$H-NMR spectra. Usual work up of an ethereal solution means washing the solution with 5% aqueous hydrochloric acid, water, a 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulfate and evaporation of the solvent *in vacuo*.

Cleavage of Epoxides *IIIa* and *IVa*

The epoxide (200 mg) was dissolved in dioxane (8 ml), water (0·5 ml) was added and the mixture was treated with 72% aqueous perchloric acid (0·3 ml) or 48% aqueous hydrobromic acid (0·5 ml) at room temperature for 20 min. The mixture was diluted with ether and water, the organic layer was washed ten times with water, dried with sodium sulfate and the solvent was evaporated. The residue was chromatographed on four preparative silica gel plates (20 × 20 cm) using a mixture of light petroleum, ether and acetone (85 : 10 : 5) for development. Corresponding zones were collected, eluted with ether, the solvent was evaporated *in vacuo* and the residue was dried in vacuum desiccator overnight. The yields of products are given in Table I. The compounds were crystallized from a mixture of acetone, methanol and water or from a mixture of chloroform and methanol. The $^1$H-NMR data of the products are given in Table II and the analytical and physical data in the Table III.

5β-Cholestane-5,6α,19-triol 6,19-Diacetate (*XI*)

The diol *Xa* (40 mg) was dissolved in pyridine (1 ml) and treated with acetic anhydride (0·3 ml) at room temperature for 2 days. The mixture was decomposed with ice and water, the product was taken up in ether and the ethereal solution was worked up as usual. The residue was dissolved in a mixture of light petroleum and benzene (2 : 1) and filtered through a little column of aluminum oxide. The eluate was evaporated to yield the oily acetate *XI* (38 mg), $[\alpha]_D^{20}$ +40° (*c* 3·8). $^1$H-NMR spectrum: 0·63 (3 H, s, 18-H), 2·03 (3 H, s, $CH_3CO_2$—$C_{19}$), 2·08 (3 H, s, $CH_3CO_2$—$C_{(6)}$), 4·25 (2 H, s, 19-H), 5·22 (1 H, dd, $J_{6\beta,7\beta}$ = 4·5 Hz, $J_{6\beta,7\alpha}$ = 12 Hz, 6β-H). For $C_{31}H_{52}O$ (504·8) calculated: 73·77% C, 10·38% H; found: 73·66% C, 10·52% H.

5α-Cholestane-5,6β,19-triol 6,19-Diacetate (*XIV*)

The diol *XIIa* (35 mg) was dissolved in pyridine (1 ml), treated with acetic anhydride (0·3 ml) and worked up as given in previous experiment to yield the oily diacetate *XIV* (31 mg), $[\alpha]_D^{20}$ —18° (*c* 3·1). $^1$H-NMR spectrum: 0·65 (3 H, s, 18H), 2·03 (3 H, s, $CH_3CO_2$—$C_{(19)}$), 2·08 (3 H, s, $CH_3CO_2$—$C_{(6)}$), 4·35 (1 H, d, *J* = 12 Hz, 19-H), 4·60 (1 H, d, *J* = 12 Hz, 19-H), 4·76 (1 H, m, *W* = 10 Hz, 6α-H). For $C_{31}H_{52}O_5$ (504·0) calculated: 73·77% C, 10·38% H; found: 73·65% C, 10·46% H.

19-Methoxy-4-cholesten-6-one (*XV*)

*a*) The alcohol *IX* (20 mg) was dissolved in dichloromethane (2 ml) and stirred with pyridinium chlorochromate (40 mg) at room temperature for 2 h. The mixture was filtered through a column of aluminum oxide (2 g). The filtrate was evaporated and the residue crystallized from a mixture of acetone, methanol and water to afford the ketone *XV* (13 mg), m.p. 91—93°C, $[\alpha]_D^{20}$ +39° (*c* 2·0). $^1$H-NMR spectrum: 0·72 (3 H, s, 18-H), 3·22 (3 H, s, $CH_3O$), 3·20 (1 H, d, *J* = 10 Hz, 19-H), 3·51 (1 H, d, *J* = 10 Hz, 19-H), 6·49 (1 H, m, *W* = 14 Hz, 4-H). IR spectrum: 1113, 1630, 1689, 2812 cm$^{-1}$. For $C_{28}H_{46}O_2$ (414·7) calculated: 81·10% C, 11·18% H; found: 81·02% C, 11·21% H.

*b*) The hydroxy ketone *XVI* (20 mg) was dissolved in pyridine (1 ml) and treated with thionyl chloride (0·1 ml) at 0°C for 15 min. The mixture was decomposed with ice and water, the product was extracted with ether and the ethereal solution was worked up as usual. The residue was crystallized from a mixture of acetone, methanol and water to give the unsaturated ketone *XV* (11 mg) identical with the compound prepared in the previous experiment. M.p. 93—94°C, $[\alpha]_D^{20}$ +42° (*c* 2·1).

5-Hydroxy-19-methoxy-5α-cholestan-6-one (*XVI*)

The diol *VIa* (50 mg) was dissolved in dichloromethane (3 ml) and stirred with pyridinium chlorochromate (100 mg) at room temperature for 2 h. The solution was filtered through a column of aluminum oxide (3 g), the filtrate evaporated and the residue crystallized from a mixture of acetone, methanol and water to yield the hydroxy ketone *XVI* (37 mg), m.p. 166—167°C, $[\alpha]_D^{20}$ −32° (*c* 2·4). $^1$H-NMR spectrum: 0·67 (3 H, s, 18-H), 3·19 (3 H, s, $CH_3O$), 3·34 (1 H, d, $J$ = 11 Hz, 19-H), 3·47 (1 H, d, $J$ = 11 Hz, 19-H). IR spectrum: 1113, 1705 sh, 1712, 2812, 3450, 3600 cm$^{-1}$. For $C_{28}H_{48}O_3$ (432·7) calculated: 77·73% C, 11·18% H; found: 77·59% C, 11·15% H.

*The analyses were carried out in the Analytical Laboratory of this Institute (head Dr J. Horáček). The* IR *spectra were recorded by Mrs K. Matoušková and by Mr P. Formánek and interpreted by Dr S. Vašíčková. The* $^1$H-NMR *spectra were recorded by Mrs J. Jelínková and M. Snopková. The mass spectra were recorded and interpreted by Dr F. Tureček, J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Czechoslovak Academy of Sciences, Prague.*

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