PARTICIPATION OF THE OXYGEN-CONTAINING SUBSTITUENT IN ALKALINE SAPONIFICATION OF 3,4a-DISUBSTITUTED 4,4-DIMETHYL-5,6β-EPOXY-A-HOMO-5β-CHOLESTANE DERIVATIVES

Helena VELGOVÁ

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

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Alkaline saponification of the 3-acetoxy group in 3,4a-disubstituted 4,4-dimethyl-5,6β-epoxy--A-homo-5β-cholestane derivatives *I*—*VI* was studied. It was found that the 3α- and 4aα-hydroxy groups participated in the cleavage of the 5β,6β-epoxide ring in the derivatives *II*—*IV*: the $5(O)^n$ participation by the 3α-hydroxy group (the derivatives *III* and *IV*) led to formation of the transannular 3α,5α-epoxides *XII* and *XIV* whereas the participation by the 4aα-hydroxy group (the derivatives *II* and *IV*) gave rise to the 4aα,5α-epoxides *IX* and *XV*. The $5(O)^n$ participation by the 3α-hydroxy group predominated over the participation by the 4aα-hydroxy group. In the case of the 4a-keto epoxides *V* and *VI* the retroaldol–aldol type isomerization led to formation of 3β-hydroxy-4,4-dimethyl-5,6β-epoxy-A-homo-5β-cholestan-4a-one as the main component of the equilibration mixtures.

In our preceding paper[1] we have found that in alkaline saponification of 3α-acetoxy--4,4-dimethyl-5,6β-epoxy-A-homo-5β-cholestane the 3α-substituent participated through the $5(O)^n$ process (for notation see ref.[2]) in the cleavage of the 5β,6β-epoxide ring under formation of the transannular 3α,5α-epoxide. In connection with our investigations it was of interest to examine the course of analogous saponification of some 3,4a-disubstituted 4,4-dimethyl-5,6β-epoxy-A-homo-5β-cholestane derivatives. This paper concerns alkaline saponification of the 3-acetoxy group in 4,4-dimethyl-5,6β-epoxy-A-homo-5β-cholestane derivatives bearing the hydroxy or carbonyl group in the position 4a.

The already known[3] epoxides *I*—*VI* were treated with potassium hydrogen carbonate in refluxing aqueous methanol. The yields of the main products of the reaction of the derivatives *I*—*IV* bearing the hydroxy group in the position 4a are given in Table I. As evident from Table I under these conditions not only the 3α-substituent but also the 4aα-hydroxy group can participate in the cleavage of the 5β,6β-epoxide ring. As it was expected no opening of the 5β,6β-epoxide ring was observed in the case of the 3β,4aβ-disubstituted epoxide *I* and the known[3] 3β,4aβ-diol *VII* was obtained as the main product. The 4aα-hydroxy group participated in the cleavage of the 5β,6β-

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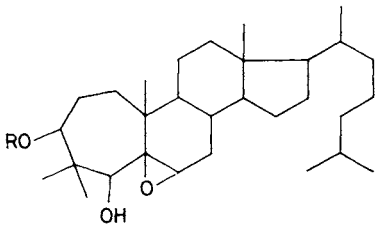
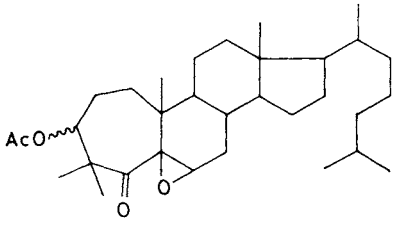
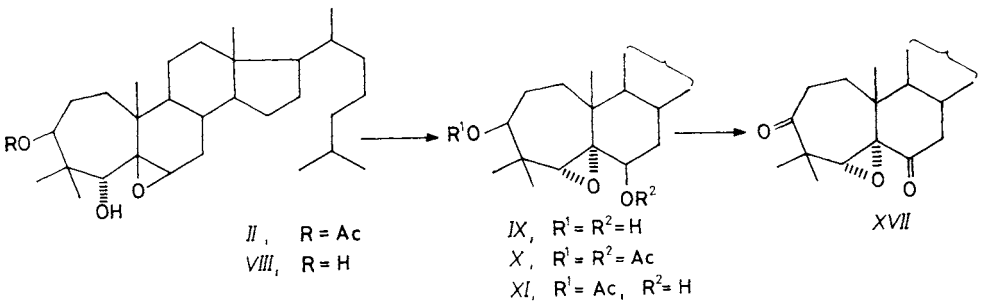
-epoxide ring in the 3β,4aα-disubstituted epoxide *II* under formation of the 4aα,5α--epoxide *IX* only to a small extent whereas the main product of the reaction was the known[3] 3β,4aα-diol *VIII*. In the case of the 3α,4aβ-disubstituted epoxide *III* a product of the 5(O)^n participation by the 3α-substituent, *i.e.* the known[4] transannular 3α,5α--epoxide *XII*, was formed in only 12% yield whereas the main product was the known[3] 3α,4aβ-diol *XIII*. On the contrary, the 3α-substituent in the 3α,4aα-disubstituted epoxide *IV* participated in the cleavage of the 5β,6β-epoxide ring under formation of the known[4] transannular 3α,5α-epoxide *XIV* very easily whereas a product of the participation by the 4aα-hydroxy group, *i.e.* the 4aα,5α-epoxide *XV*, was formed only



I, R = Ac
VII, R = H



V, β - OAc
VI, α - OAc



II, R = Ac
VIII, R = H

IX, $R^1 = R^2 = H$
X, $R^1 = R^2 = Ac$
XI, $R^1 = Ac$, $R^2 = H$

XVII

as a minor product. Therefore, in the epoxide *IV* the 3α-substituent competes in participation with the 4aα-hydroxy group, the 5(O)^n participation by the 3α-substituent being predominant. The compounds *XIV* and *XV* were formed in nearly the same ratio (4 : 1) also on treatment of the epoxide *IV* with potassium hydroxide in refluxing aqueous methanol whereas under the same conditions the epoxide *II* as well as the 3β,4aα-diol *VIII* could be almost quantitatively converted into the 4aα,5α-epoxide *IX*. It indicates that in the case of the participation by the 4aα-hydroxy group a reactive species, *i.e.* the 4aα-alkoxide ion, needs more alkaline conditions to be formed and that, in comparison with the results given in Table I, in the 3,4aα--disubstituted 5β,6β-epoxides the 5(O)^n participation by the 3α-alkoxide ion is predominant over the participation by the 4aα-alkoxide ion. The decrease in the ability

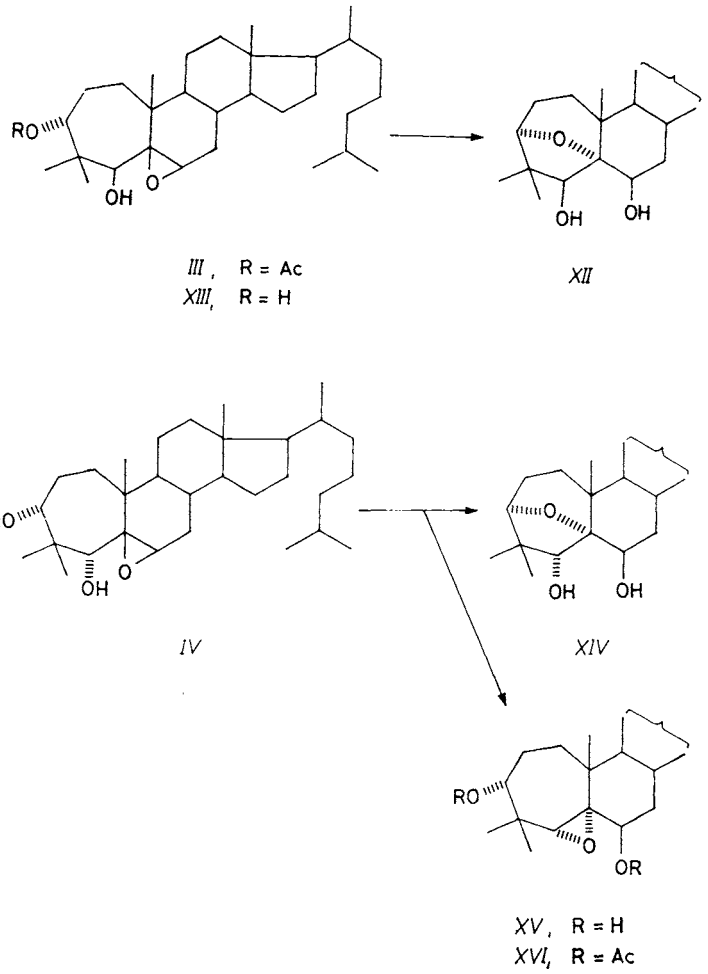


TABLE I

Yields (in % of the total yield) of the products of saponification of the acetates *I*—*IV*

Compound	5β,6β-Epoxide	3α,5α-Epoxide	4aα,5α-Epoxide	Total yield	Ref.
I	96 (*VII*)	—	—	98	3
II	73 (*VIII*)	—	20 (*IX*)	98	4
III	14 (*III*)	12 (*XII*)	—	98	4
	72 (*XIII*)				3
IV	—	82 (*XIV*)	20 (*XV*)	98	4

of the 3α-substituent to participate in the cleavage of the 5β,6β-epoxide ring in the 4aβ-hydroxy derivative *III* in comparison with the 4aα-hydroxy derivative *IV* could be most probably explained by a strong steric interaction between the relatively bulky solvated 4aβ-alkoxide ion, which could be also acting inductively in destabilizing a developing positive charge at the $C_{(5)}$-carbon atom, and the 1β-hydrogen atom in the transition state of the transformation to the transannular 3α,5α-epoxide *XII*. The structures of the 4aα,5α-epoxides *IX* and *XV* were confirmed by their transformation to the same diketone *XVII* and by the ^{1}H NMR spectra of the corresponding diacetoxy derivatives *X* and *XVI*. In accord with the suggested structures the ^{1}H NMR spectra of the compounds *X* and *XVI* display signals of one epoxidic proton (a singlet at $\delta = 2{\cdot}75$ in *X* and $\delta = 2{\cdot}275$ in *XVI*) and of two CH—$OCOCH_3$ protons (multiplets at $\delta = 4{\cdot}22$ and $\delta = 4{\cdot}60$ in *X* and $\delta = 4{\cdot}22$ and $\delta = 4{\cdot}72$ in *XVI*). In line with the proposed structure of the 4aα,5α-epoxide *XV* is also the fact that the infrared spectrum of this compound demonstrates the presence of an intramolecular hydrogen bonding ($\nu_{OH(free)} = 3\,622\ cm^{-1}$, $\nu_{OH(bonded)} = 3\,545\ cm^{-1}$).

In our preceding paper[4] we have found that on epoxidation 3β-acetoxy-4,4-dimethyl-A-homo-5-cholesten-4aα-ol gave, along with the 5β,6β-epoxide *II*, also a small amount of another epoxide (14% yield) which was now proved to be 3β-acetoxy-4,4-dimethyl-4aα,5-epoxy-A-homo-5α-cholestan-6β-ol (*XI*) by its transformation to the diacetoxy derivative *X*. The fact that the epoxide *II* when treated with 3-chloroperbenzoic acid in chloroform afforded, along with the unchanged starting 5β,6β-epoxide *II*, also the 4aα,5α-epoxide *XI* (19% yield) indicates that the epoxide *XI* is a product of the participation by the 4aα-hydroxy group in the acid catalyzed opening of the 5β,6β-epoxide ring in the epoxide *II*. Under the same conditions the epimeric 3α-acetoxy 5β,6β-epoxide *IV* was recovered unchanged.

Alkaline saponification of the 3-acetoxy group in the 4a-keto epoxides *V* and *VI* with potassium hydrogen carbonate in refluxing aqueous methanol afforded inseparable mixtures of the corresponding 3β- and 3α-hydroxy derivatives which on acetylation gave the 3β and 3α-acetoxy derivatives *V* and *VI* in a 9 : 1 ratio in both cases. The epimerization of the 3-substituent in the 4a-keto epoxides *V* and *VI* could be most probably explained by the retroaldol–aldol type isomerization.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured in chloroform, unless stated otherwise. The infrared spectra were recorded on a Zeiss UR 20 spectrometer in chloroform, unless stated otherwise. The ^{1}H NMR spectra were recorded on a spectrometer Tesla B 476 (60 MHz) in deuteriochloroform with tetramethylsilane as internal standard at 22°C. Chemical shifts are given in δ-scale. The identity of samples prepared by different routes was checked by mixture melting point determination and infrared spectra. The term "usual work-up procedure" means that the solution was washed with 5% hydrochloric acid, 5% aqueous solution of potassium hydrogen carbonate, water, dried over sodium sulfate and the

solvent was evaporated *in vacuo*. The crude residue was purified by preparative thin-layer chromatography on silica gel plates (20 × 20 × 0·07 cm) in light petroleum–ether (6 : 4), unless stated otherwise. The corresponding zones were combined, eluted with ether and the solvent was evaporated under reduced pressure.

Alkaline Saponification of Acetates *I*—*VI*

An aqueous solution of potassium hydrogen carbonate (130 mg in 1 ml H_2O) was added to a solution of the acetate (130 mg) in methanol (13 ml) and the mixture was refluxed for 4 h (in the case of *I*—*IV*) or 2 h (in the case of *V* and *VI*). The mixture was then poured into water and the product was extracted with ether. The extract was washed with water, dried over sodium sulfate and the solvent was evaporated *in vacuo*. The residue was preparatively chromatographed on 3 plates of silica gel. The yields of the main products of saponification of the acetates *I*—*IV* are given in Table I. In the case of the acetates *V* and *VI* the preparative TLC afforded the inseparable mixture of the corresponding 3β- and 3α-hydroxy derivatives which was acetylated with acetic anhydride (0·1 ml) in pyridine (3 ml) overnight. The usual work-up gave a product which was preparatively chromatographed on 3 plates of silica gel in light petroleum–ether (8 : 2). The corresponding zones with the lipophilic component were combined and worked up affording the acetate *V*. The corresponding combined zones with the polar component gave after working up the acetate *VI*. The acetates *V* and *VI* were obtained in a 9 : 1 ratio.

4,4-Dimethyl-4aα,5-epoxy-A-homo-5α-cholestane-3β,6β-diol (*IX*)

An aqueous solution of potassium hydroxide (50 mg in 0·5 ml H_2O) was added to a solution of the epoxide *VIII* (50 mg) in methanol (10 ml) and the mixture was refluxed for 1 h and then poured into water. A separated product was collected by suction, washed with water, dissolved in methanol and the solvent was evaporated *in vacuo*. The residue (46 mg) was crystallized from ethanol–dioxane to give 32 mg of the diol *IX*, m.p. 275—278°C. IR spectrum (KBr pellet): 3 435, 3 360 (hydroxyl), 1 054, 1 035, 1 022, 961, 930 (ether) cm^{-1}. For $C_{30}H_{52}O_3$ (460·7) calculated: 78·20% C, 11·38% H; found: 78·06% C, 11·19% H.

4,4-Dimethyl-4aα,5-epoxy-A-homo-5α-cholestane-3β,6β-diol 3,6-Diacetate (*X*)

a) The diol *IX* (50 mg) was acetylated with acetic anhydride (0·1 ml) in pyridine (2 ml) overnight. The usual work-up afforded 50 mg of a product which was crystallized from methanol to give 35 mg of the diacetate *X*, m.p. 138—140°C, $[\alpha]_D^{20}$ +30° (*c* 0·5). IR spectrum: 1 730, 1 249, 1 022 (acetate), 961, 950 (ether) cm^{-1}. ^1H NMR spectrum: 0·69 (s, 18-H), 0·85 (d, 21 + 26 + + 27-H, J = 6 Hz), 1·05, 1·15, 1·23 (s, 19-H; s, 4,4-dimethyl), 1·98 (s, acetate), 2·03 (s, acetate), 2·73 (bs, 4aβ-H), 4·22 (mt, 6α-H), 4·60 (mt, 3α-H). For $C_{34}H_{56}O_5$ (544·8) calculated: 74·96% C, 10·36% H; found: 74·87% C, 10·24% H.

b) The alcohol *XI* (50 mg) was acetylated with acetic anhydride (0·1 ml) in pyridine (2 ml) overnight. The usual work-up afforded 50 mg of a product which was crystallized from methanol to yield 31 mg of the diacetate *X*, m.p. 138—140°C, $[\alpha]_D^{20}$ +30° (*c* 0·5).

4,4-Dimethyl-4aα,5-epoxy-A-homo-5α-cholestane-3β,6β-diol 3-Acetate (*XI*)

3-Chloroperbenzoic acid (160 mg) was added to a solution of the epoxide *II* (160 mg), ref.[4], in chloroform (10 ml). The mixture was allowed to stand at room temperature for 2 h, then poured into water and a product was extracted with ether. The extract was washed with a saturated

aqueous solution of potassium carbonate, water, dried over sodium sulfate and the solvent was evaporated *in vacuo*. The residue (160 mg) was preparatively chromatographed on 3 plates of silica gel in light petroleum–ether (8 : 2). The corresponding zones with the lipohilic component were combined and worked up to give 120 mg of the starting epoxide *II*, ref.[4], m.p. 127–129°C. The corresponding combined zones with the polar component gave after working up 30 mg of the epoxide *XI* which was crystallized from methanol (18 mg), m.p. 193–195° C, $[\alpha]_D^{20}$ +28° (*c* 0·5). IR spectrum: 3 615 (hydroxyl), 1 728, 1 247, 1 024 (acetate), 1 048, 966, 946 (ether) cm^{-1}. ^1H NMR spectrum: 0·70 (s, 18-H), 0·86 (d, 21 + 26 + 27-H, $J = 6$ Hz), 1·17, 1·23 (s, 19-H; s, 4,4-dimethyl), 2·00 (s, acetate), 2·45 (s, 4aβ-H), 3·07 (mt, 6α-H), 4·63 (mt, 3α-H). For $C_{32}H_{54}O_4$ (502·75) calculated: 76·44% C, 10·83% H; found: 76·23% C, 10·67% H.

4,4-Dimethyl-4aα,5-epoxy-A-homo-5α-cholestane-3α,6β-diol (*XV*)

An aqueous solution of potassium hydroxide (100 mg in 1 ml H_2O) was added to a solution of the epoxide *IV* (135 mg), ref.[4], in methanol (15 ml) and the mixture was refluxed for 1 h and then poured into water. A product was extracted with ether, the extract was washed with water, dried over sodium sulfate and the solvent was evaporated *in vacuo*. The residue (124 mg) was preparatively chromatographed on 3 plates of silica gel. The corresponding zones with the lipophilic component were combined and worked up to give 81 mg of the 3α,5α-epoxide *XIV*, ref.[4], which resisted to all crystallization attempts, $[\alpha]_D^{20}$ −14° (*c* 0·5). The corresponding combined zones with the polar component afforded after working up 47 mg of the epoxide *XV* which was crystallized from heptane (21 mg), m.p. 214–216°C, $[\alpha]_D^{20}$ +21° (dioxane, *c* 0·5). IR spectrum: 3 610 (hydroxyl), 1 045, 1 000, 935, (ether) cm^{-1}. IR spectrum (tetrachloromethane): 3 622, 3 545 (hydroxyl) cm^{-1}. For $C_{30}H_{52}O_3$ (460·7) calculated: 78·20%C, 11·38% H; found: 78·00% C, 11·23% H.

4,4-Dimethyl-4aα,5-epoxy-A-homo-5α-cholestane-3α,6β-diol 3,6-Diacetate (*XVI*)

The diol *XV* (55 mg) was acetylated with acetic anhydride (0·5 ml) in pyridine (3 ml) for 3 days. The usual work-up afforded 52 mg of a product which was preparatively chromatographed on one plate of silica gel in light petroleum–ether (9 : 1). The corresponding zone gave after working up 45 mg of the diacetate *XVI* which was crystallized from methanol (28 mg), m.p. 134–136°C, $[\alpha]_D^{20}$ −7° (*c* 0·5). IR spectrum: 1 728, 1 248, 1 030 (acetate), 997, 981, 963, 952 (ether) cm^{-1}. ^1H NMR spectrum: 0·72 (s, 18-H), 0·85 (d, 21 + 26 + 27-H, $J = 6$ Hz), 0·99, 1·15, 1·18 (s, 19-H; s, 4,4-dimethyl), 2·05 (s, acetate), 2·725 (bs, 4aβ-H), 4·22 (mt, 6α-H), 4·72 (mt, 3β-H). For $C_{34}H_{56}O_5$ (544·8) calculated: 74·96% C, 10·36% H; found: 74·75% C, 10·23% H.

4,4-Dimethyl-4aα,5-epoxy-A-homo-5α-cholestane-3,6-dione (*XVII*)

a) Chromium trioxide (50 mg) was added to a solution of the diol *IX* (50 mg) in pyridine (2 ml) and the mixture was allowed to stand at room temperature overnight. The usual work-up afforded 50 mg of a product which was preparatively chromatographed on one plate of silica gel in light petroleum–ether (8 : 2). The corresponding zone gave after working up 43 mg of the dione *XVII* which was crystallized from methanol (26 mg), m.p. 172–173°C, $[\alpha]_D^{20}$ −64° (*c* 0·5). IR spectrum: 1 710 (carbonyl), 954 (epoxide) cm^{-1}. For $C_{30}H_{48}O_3$ (456·7) calculated: 78·90% C, 10·59% H; found: 78·77% C, 10·42% H.

b) The diol *XV* (50 mg) was treated with chromium trioxide (50 mg) in pyridine (2 ml) in the same manner as in the preceding procedure. The usual work-up afforded 49 mg of a product which was crystallized from methanol to give 28 mg of the dione *XVII*, m.p. 172–173°C, $[\alpha]_D^{20}$ −64° (*c* 0·5).

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