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Peracids oxidation of cholesta-5,8-dien-3β-yl acetate

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Expoxidation of cholesta-5,8-dien-3β-yl acetate (**1**) with peracids takes place preferentially at the more highly substituted Δ^8-olefinic double bond to give: (a) with monoperphthalic acid, 8α,9α-epoxycholest-5-en-3β-yl acetate (**2**) (in 39 % yield) and 9α-hydroxy-5α,6α-epoxycholest-8(14)-en-3β-yl acetate (**3**) (in 30 % yield); and (b) with *m*-chloroperbenzoic acid, the 8α,9α-epoxide **2** (64 %) and 5α,6α-epoxy derivative **3** (20 %). Some chemical transformations of the obtained epoxides are described.

Keywords: cholesta-5,8-dien-3β-yl acetate, peracid oxidations, steroidal epoxides, reactivity of.

INTRODUCTION

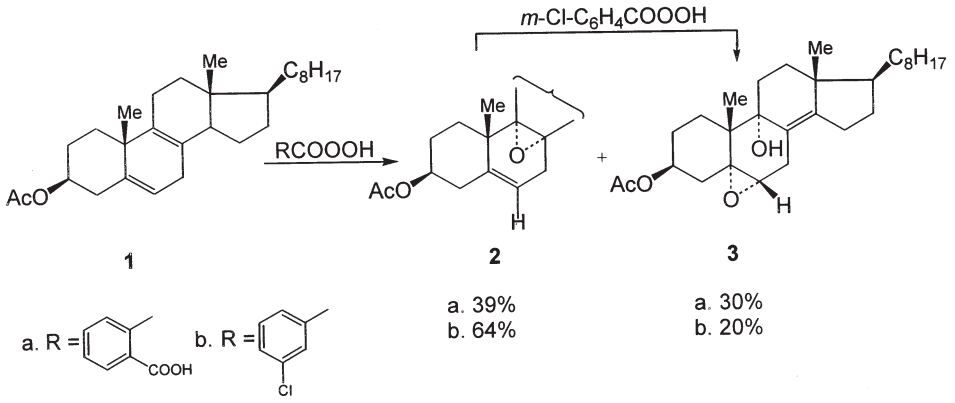
It is known that the rate of epoxidation of an olefinic double bond with peracids increases with the degree of alkyl substitution.[1] Since cholesta-5,8-dien-3β-yl acetate (**1**)[2] (Scheme 1) contains two unequally substituted (*i.e.,* the Δ^5-trisubstituted and Δ^8-tetrasubstituted) double bonds, the aim of the present work was to investigate if this compound reacts regioselectively when treated with peracids. Such a possibility would enable the preparation of some new difunctionalized steroidal derivatives.

RESULTS AND DISCUSSION

Oxidation of **1** was carried out with: (a) monoperphthalic acid in diethyl ether, and (b) with *m*-chloroperbenzoic acid in dichloromethane solution, with a slight excess of oxidant (for details see Experimental). After the usual work up, the resulting reaction mixtures were separated by column chromatography on silica gel.

It was found that in both cases two main products were obtained (Scheme 1), *i.e.,* the 8α,9α-epoxycholest-5-en-3β-yl acetate (**2**) (in (a) 39 % and (b) 64 % yield), and 9α-hydroxy-5α,6α-epoxycholest-8(14)-en-3β-yl acetate (**3**) (in (a) 30 % and (b) 20 % yield). Their structures were deduced on the basis of the following evidences.

* Serbian Chemical Society active member



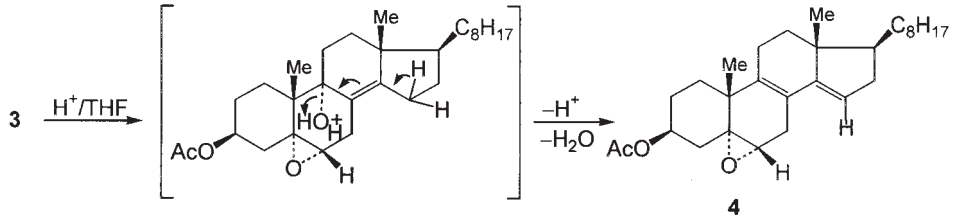
Scheme 1.

Thus, for the more mobile component **2**, microanalysis ($C_{29}H_{46}O_3$), mass spectroscopy ($M^{+\cdot} = 442$) and ^{1}H-NMR data (the appearance of a broad triplet at δ 5.25 ppm for the olefinic H–C(6) proton, and the absence of a signal at δ *ca.* 3.0 ppm for the oxirane hydrogen) indicated that it is a monoepoxide formed by epoxidation of the tetrasubstituted Δ^8-bond of diene **1**. Its 8α, 9α-stereochemistry is in accordance with the "rule of α-attack" upon steroids*

On the other hand, the more polar compound **3** ($C_{29}H_{46}O_4$; $M^{+\cdot} = 458$) was formed by reaction of both the Δ^5- and Δ^8-double bond of **1** with peracids. The ^{1}H-NMR spectrum of **3** shows a triplet at δ 2.86 ppm for the oxirane H–C(6) proton (and no signal for an olefinic hydrogen), while its IR spectrum contains a broad band between 3300–3650 cm^{-1} for a hydroxyl group.

The 9α-hydroxy derivative **3** was also obtained from epoxide **2** when it was treated with *m*-chloroperbenzoic acid in dichloromethane solution (Scheme 1).

The proposed structure of compound **3** was confirmed by its dehydration (with a catalytic amount of perchloric acid in tetrahydrofuran solution) to give the epoxy-diene



Scheme 2.

* Δ^8-Ergosteryl acetate, the Δ^5-saturated analogue of diene **1**, also gives in high yield the correponding 8α, 9α-epoxide with perbenzoic acid in benzene solution.[3]

derivative **4** (Scheme 2). Spectral data supporting this structure are given in the Experimental.

Moreover the chemical shifts of the methyl protons at C(18) and C(19) in compound **4** (0.78 and 1.20 ppm, respectively) are in complete agreement with the values calculated according to the additivity rule for the substituent effects in steroid systems (0.82 and 1.21 ppm, respectively).

From the obtained results it follows: (i) epoxidation of cholesta-5,8-dien-3β-yl acetate (**1**) with peracids takes place preferentialy at the more highly substituted Δ^8-double bond; (ii) subsequent epoxidation of Δ^5-double bond is accompanied with the transformation of the already formed 8,9-oxirane ring to the more stable allylic alcohol function*, thus giving the 9α-hydroxy-$\Delta^{8(14)}$-ene derivative **3**; (iii) the isomeric Δ^8-unsaturated 5α,6α-monoepoxide was not detected among the reaction products.

EXPERIMENTAL

General

Removal of solvents was carried out under reduced pressure. Column chromatography (CC): silica gel, 0.063–0.200 mm. TLC: control of the reaction and separation of the products on silica gel G (Stahl) with benzene/AcOEt 9:1, detection with 50 % aq. H_2SO_4 soln. M. p.: uncorrected. IR Spectra: Perkin-Elmer 337 spectrometer, ν in cm^{-1}. ^{1}H-NMR spectra: Varian FT 80A; $CDCl_3$ soln. at r.t., TMS as internal standard, δ in ppm, *J* in Hz.

Cholesta-5,8-dien-3β-yl acetate (**1**) was prepared from 7-dehydrocholesteryl acetate as described by Anastasia *et al.*[2]

Epoxidation of cholesta-5,8- dien-3β-yl acetate (1) with monoperphthalic acid

To a stirred solution of **1** (3.00 g) in diethyl ether (50 ml), monoperphthalic acid (1.4g, 1 mole equiv. +10%) in 30 ml diethyl ether was added and the mixture was stirred at room temperature for 1.5 h.It was then washed with aq. $NaHSO_4$, water, sat. aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness. The resulting mixture (3.02 g) was chromatographed on a SiO_2 column (15 g).

A complex mixture (520 mg) eluted with toluene which was not further investigated. Toluene-diethyl ether (99:1) afforded 8α9α-epoxycholest-5-en-3β-yl acetate (**2**) (1.21 g, 38.9 %), m.p. 199 °C (acetone-MeOH). IR (KBr): 3040, 1732, 1250, 840 cm^{-1}. ^{1}H-NMR: 0.70 (3H, *s*, Me(18)), 0.86 (6H, *d*, *J* = 6 Hz, Me(26), Me(27)), 0.90 (3H, *d*, *J* = 6 Hz, Me(21)), 1.24 (3H, *s*, Me(19)), 2.04 (3H, *s*, AcO), 4.80 (1H, *m*, H-C(3)), 5.25 (1H, *br.t*, *J* ≈ 2.8 Hz, H–C(6)). MS: 442 (20, M^+). Anal. Calcd. for $C_{29}H_{46}O_3$ (442.687): C 78.68, H 10.48; found C 78.50, H 10.21.

Elution with toluene-diethyl ether (98:2) afforded 9α-hydroxy-5α,6α-epoxycholest-8(14)--en-3β-yl acetate (**3**) (960 mg, 29.8 %), m.p. 150 °C (acetone-MeOH). IR (KBr): 3650–3300, 3020, 1735, 1690, 1245 cm^{-1}. ^{1}H-NMR: 0.64 (3H, *s*, Me(18)), 0.85 (6H, *d*, *J* = 6 Hz, Me(26), Me(27)), 0.88 (3H, *d*, *J* = 6 Hz, Me(21)), 1.37 (3H, *s*, Me(19)), 1.98 (3H, *s*, AcO), 2.86 (1H, *t*, *J* = 3 Hz, H–C(6)), 5.00 (1H, *m*, H–C(3)). MS: 458 (40, M^+), 440 (100, M^+–18), 398 (58, M^+–60), 380 (80, M^+–60–18). Anal. Calcd. for $C_{29}H_{46}O_4$ (458.687): C 75.94, H 10.11; found: C 75.96, H 9.92.

Epoxidation of cholesta-5,8-dien-3β-yl acetate (1) with m-*chloroperbenzoic acid*

To a stirred solution of **1** (812 mg) in dichloromethane (12.5 ml) cooled at 0 °C, *m*-chloroperbenzoic acid (500 mg, 76 %, 1 mole equiv. +10 % excess) in dichloromethane (12.5 ml) was grad-

* A similar opening of the 8,9-epoxide ring and further dehydration to the $\Delta^{8,13}$-diene system was observed upon epoxidation of Δ^8-cholestenyl acetate with perbenzoic acid in chloroform solution.[4]

ually added and the mixture kept at 0–5 ºC with stirring for 30 min. It was then diluted with diethyl ether and work up as above. The resulting mixture (820 mg) was chromatographed on a SiO_2 column as previously described to give: a complex mixture (about 50 mg), 8α9α-epoxycholest-5-en-3β-yl acetate (**2**) (585 mg, 64.0 %) and 9α-hydroxy-5α,6α-epoxycholest-8(14)-en-3β-yl acetate (**3**) (174 mg, 19.9 %).

Epoxidation of 8α9α-epoxycholest-5-en-3β-yl acetate (2) with m-*chloroperbenzoic acid*

A solution of **2** (165 mg) in dichloromethane (5 ml) cooled at 0 ºC was treated with *m*-chloroperbenzoic acid (100 mg, 76 %) in dichloromethane (5 ml). The mixture was kept at 0–5 ºC with stirring for 30 min and worked up in the usual way to give 9α-hydroxy-5α,6α-epoxycholest-8(14)-en-3β-yl acetate (**3**) (170 mg, 99.4 %), m.p. 150 ºC (acetone–MeOH), undepressed by admixture with an authentic sample.

Dehydration of 9α-hydroxy-5α,6α-epoxycholest-8(14)-en-3β-yl acetate (3)

To a cooled (0 ºC) and stirred solution of **3** (100 mg) in tetrahydrofuran (6 ml), a drop of $HClO_4$ was added and the stirring continued for 10 min. The mixture was worked up in the usual way to give 5α,6α-epoxycholest-8,14-dien-3β-yl acetate (**4**) (96 mg, quant.) m.p. 140–143 ºC (acetone-MeOH). IR (KBr): 3050, 1732, 1725, 1258, 1245, 800 cm^{-1}. ^{1}H-NMR: 0.78 (3H, *s*, Me(18)), 0.86 (6H, *d*, *J* = 6.5 Hz, Me(26), Me(27)), 0.90 (3H, *d*, *J* = 6.5 Hz, Me(21)), 1.20 (3H, *s*, Me(19)), 2.03 (3H, *s*, AcO), 3.10 (1H, *br.s*, H–C(6)), 5.00 (1H, *m*, H–C(3)), 5.42 (1H, *br.t*, H–C(15)). Anal. Calcd. for $C_{29}H_{44}O_3$ (440.671): C 79.04, H 10.07; found: C 78.93, H 9.86.

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I Z V O D

ОКСИДАЦИЈА ХОЛЕСТА-5,8-ДИЕН-3β-ИЛ АЦЕТАТА СА ПЕРКИСЕЛИНАМА

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Епоксидација холеста-5,8-диен-3β-ил ацетата (**1**) са перкиселинама првенствено се одвија на више супституисаној Δ^8-олефинској двогубој вези при чему се добија: (а) са моноперфталном киселином, 8α,9α-епоксихолест-5-ен-3β-ил ацетат (**2**) (у преносу од 39 %) и 9α-хидрокси-5α,6α-епоксихолест-8(14)-ен-3β-ил ацетат (**3**) (у преносу од 30 %); и (б) са *m*-хлорпербензоевом киселином, 8α,9α-епоксид **2** (у преносу од 64 %) и 5α,6α-епокси дериват **3** (у преносу од 20 %). Описане су и неке хемијске трансформације добијених епоксида.

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