Epoxidation and Baeyer–Villiger Oxidation of γ-Hydroxy-αβ-unsaturated Ketones on Exposure to *m*-Chloroperbenzoic Acid

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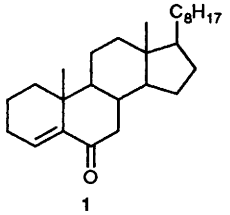
Treatment of 3β- and 3α-hydroxy-(acetoxy-)cholest-4-en-6-one and of 6β-and 6α-hydroxy-(acetoxy-)cholest-4-en-3-one with MCPBA gives two types of product, depending on the initial site of the peroxy acid attack. Attack at the carbonyl group gives a Baeyer–Villiger rearrangement leading first to enol lactones and then by epoxidation of the latter to epoxy lactones. Alternatively, attack at the double bond gives epoxy ketones which can subsequently undergo a Baeyer–Villiger rearrangement leading to epoxy lactones. With one exception (3α-hydroxycholest-4-en-6-one), the Baeyer–Villiger oxidation of the enone is the dominant process. Epoxidation of the double bond is suppressed in the presence of an axial 3α- or 6β-acetoxy group.

Two different processes occur upon treatment of αβ-unsaturated ketones with a peroxy acid in a suitable organic solvent. Attack at the carbonyl group, followed by Baeyer–Villiger rearrangement leads to the initial formation of enol esters (enol lactones in the case of cyclic structures). Alternatively, attack at the conjugated double bond leads to the formation of epoxy ketones. Under these conditions, the dominant process is usually that leading to the rearrangement,[1] although reactions in which epoxy ketones are formed are also known.[2] Once formed, the enol lactones can undergo epoxidation to the corresponding epoxy lactones. Conversely, the epoxy ketones can undergo a Baeyer–Villiger rearrangement[3] leading to the same epoxy lactones.

The present work deals with the influence of allylic, axial and equatorial hydroxy and acetoxy groups, on the behaviour of two steroidal enones in the presence of *m*-chloroperbenzoic acid (MCPBA). Our results are compared with those obtained by earlier workers who investigated the behaviour of the corresponding unsubstituted enones, cholest-4-en-6-one[4] and cholest-4-en-3-one.[4,5]



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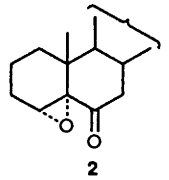

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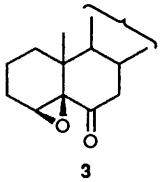

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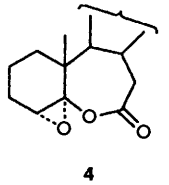

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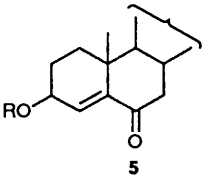
Cerny and co-workers[4] obtained by treatment of cholest-4-en-6-one **1** with MCPBA the epoxy ketones **2** (28%) and **3** (22%), and the epoxy lactone **4** (4%). The latter may have its origin in one of the two epoxy ketones **2** or **3** which underwent a Baeyer–Villiger rearrangement, or alternatively, from an enol lactone obtained by direct rearrangement of compound **1** and subsequent epoxidation. Unfortunately, the relative contributions of these two processes to the outcome of the reaction cannot be assessed because the fate of almost half of the starting material is unclear.[4]

The configuration of the epoxy group in compound **4** was not determined. The NMR data obtained in our investigation allow the assignment of the 4α,5α-configuration to the above group. Thus, subtraction of the chemical shift of 4β-H in epoxy lactone **9a** (δ 3.36) from the chemical shift of 4β-H in 4α,5α-epoxy-3β-hydroxycholestan-6-one[6] (δ 3.53) gives Δδ +0.17. The following results were obtained by similar subtractions in related compounds.

Δ[δ 4β-H (**2**) − δ 4ξ-H (**4**)]	= +0.17	Ref. 4
Δ[δ 4β-H (**16**) − δ 4β-H (**19a**)]	= +0.20	This work
Δ[δ 4α-H (**6a**) − δ 4α-H (**8a**)]	= −0.38	This work
Δ[δ 4α-H (**17**) − δ 4α-H (**20a**)]	= −0.45	This work

Treatment of 3β-hydroxycholest-4-en-6-one **5a** with 1.1 equiv. MCPBA in benzene solution for 2 days at room temperature gave two major products, the known[7] 3β-hydroxy-4β,5β-epoxycholestan-6-one **6a** (32%) [δ_H 3.25 (d, *J* 3.8, epoxidic 4-H)] and the enol lactone **7a** (57%) [δ_H 5.53 (d, *J* 4



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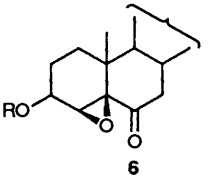

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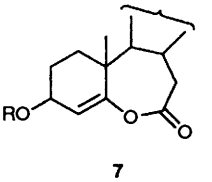

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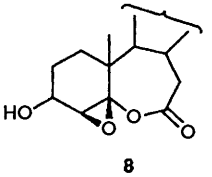

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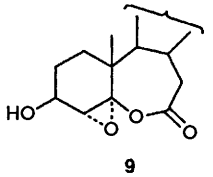

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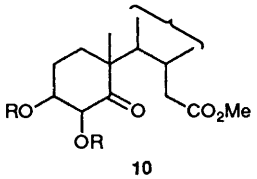
a, R = H; **b**, R = Ac

vinylic 4-H)], accompanied by a little of the 4β,5β-epoxy lactone **8a** (5%) [δ_H 3.63 (d, *J* 3, epoxidic 4-H)]. Exposure of the epoxy ketone **6a** to MCPBA for 20 h gave the same epoxy lactone **8a** (75%); similar treatment of the enol lactone **7a** gave non-stereoselective formation of a *ca.* 1:1 mixture of the epoxy lactones **8a** (4β,5β-epoxy) and **9a** (4α,5α-epoxy), the latter being characterised by a slightly broadened singlet at δ_H 3.36. It is noteworthy that epoxidation of C(4)=C(5) in **5a** resulted only in the epoxy ketone **6a** in which the epoxide is *cis* with respect to 3β-OH, in contrast to epoxidation of the enone **1** which afforded the two stereoisomeric epoxy ketones **2** and **3**. The relative amounts of compounds **6a**, **7a** and **8a** obtained directly

from compound **5a**, clearly point towards a higher rate of the Baeyer–Villiger oxidation, as compared to that of the epoxidation.

The course of events is different when 3β-acetoxycholest-4-en-6-one **5b** is exposed to MCPBA. The reaction is significantly slower: after 36 h *ca.* 30% of compound **5b** remained unchanged. The major product is the enol lactone 3β-acetate **7b** (55%), accompanied by only 5% of 3β-acetoxy-4β,5β-epoxycholestan-6-one **6b**. Whereas epoxidation with MCPBA of 3β-acetoxycholest-4-ene[8] yields only the corresponding 4α,5α-epoxide, that obtained by epoxidation of either compound **5a** or **5b** has the same 4β,5β configuration as obtained by H_2O_2/OH^- treatment of **5b**.[9]

The enol lactone and epoxy lactone structures assigned to compounds **7** and **8**, respectively, were confirmed by the following transformations. Treatment of **8a** with 5% methanolic NaOH afforded methyl 5,6-seco-3β,4β-dihydroxy-5-oxocholestan-6-oate **10a** which was acetylated to the corresponding 3,4-



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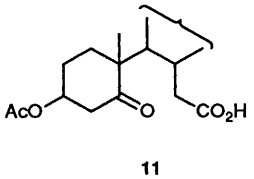

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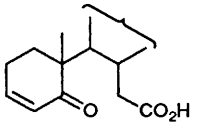

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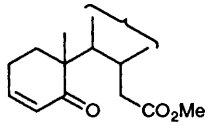

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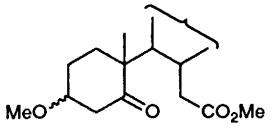

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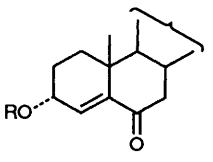
a, R = H; **b**, R = Ac

diacetate **10b**. The enol lactone **7b** (3β-acetoxy-6-oxa-7a-homocholest-4-en-7-one)* was transformed on silica gel into 5,6-seco-3β-acetoxy-5-oxocholestan-6-carboxylic acid **11**, accompanied by the product of β-elimination of AcOH **12**. In compound **11**, the 4-methylene group gave a characteristic ABX pattern in the NMR spectrum: δ_H 3.21 (dd, *J* 14.5, 4.3, H_A) and 2.43 (d, *J* 14.5, H_B); these assignments were confirmed by double irradiation. Compound **12**, upon treatment with methanol containing a trace of toluene-*p*-sulfonic acid, was transformed into two methyl esters: compound **13** in which only esterification occured (ester-type MeO signal at δ_H 3.57) and compound **14** in which the esterification was accompanied by a conjugate Michael type addition of methanol in ring A (MeO signals at δ_H 3.57 and 3.26). The same mixture of compounds **13** and **14** was obtained directly from **7b** by treatment with 5% methanolic NaOH.

The next system to be investigated was the stereoisomeric 3α-hydroxycholest-4-en-6-one **15a** in which the 3-OH group is quasi-axial. Treatment of **15a** with MCPBA for 20 h at room temperature resulted almost exclusively in products of epoxidation, 3α-hydroxy-4α,5α-epoxy- **16** (45%) and 3α-hydroxy-



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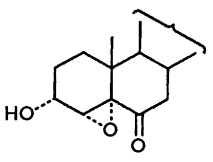

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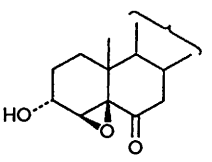

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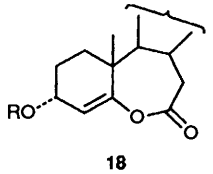

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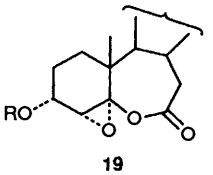

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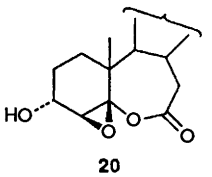

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a, R = H; **b**, R = Ac

4β,5β-epoxycholestan-6-one **17** (25%). Approximately 25% of the starting compound **15a** remained unchanged. The epoxy ketone **17** was alternatively obtained by treatment of the enone **15a** with alkaline H_2O_2. When the reaction time with MCPBA was longer (2 days), only traces of the epoxy ketones **16** and **17** were obtained: they underwent a Baeyer–Villiger oxidation to the stereoisomeric epoxy lactones **19** (4α,5α-epoxy) (60%) and **20** (4β,5β-epoxy) (20%); the enol lactone **18a** (*ca.* 20%) was also obtained.

The structure assigned to the epoxy lactone **20** was confirmed by its preparation from the epoxy ketone **17**, by treatment with MCPBA. In the epoxy lactone **19**, the epoxidic 4β-H is shifted downfield (δ 3.60) with respect to the same signal in the epoxy ketone **16**, whereas in the epoxy lactone **20**, the epoxidic 4α-H is shifted upfield (δ 3.43) with respect to the corresponding signal in the epoxy ketone **17**. Such reverse shifts probably arise from conformational changes of the flexible seven-membered ring present.

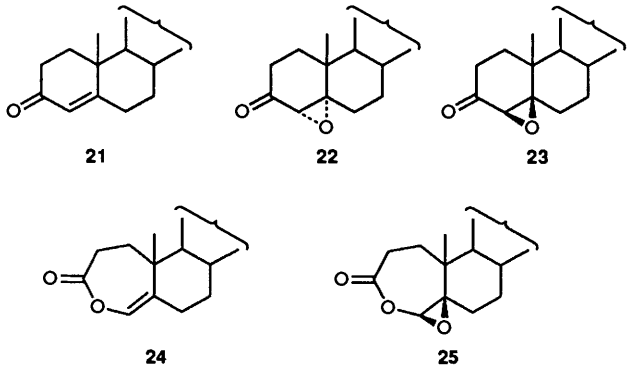
It is obvious that one of the major differences in the behaviour of compounds **5a** and **15a** is that in the former, the Baeyer–Villiger rearrangement prevails over the epoxidation process, whereas in the latter the opposite results are obtained. Furthermore, direct epoxidation with MCPBA of **5a**, in which the 3β-OH is quasi-equatorial, results in the 4β,5β-epoxide **6a**, while epoxidation of **15a**, in which the 3α-OH is quasi-axial, results in a 2:1 mixture of 4α,5α- **16** and 4β,5β-epoxide **17**.

Treatment of 3α-acetoxycholest-4-en-6-one **15b** with MCPBA for 2 days at room temperature leads to results the reverse of those obtained with compound **15a**. Thus, the epoxidation is slowed to such an extent that the only reaction taking place is the Baeyer–Villiger oxidation leading to the enol lactone **18b** (65%); *ca.* 30% of the starting compound **15b** remained unchanged. Attempted epoxidation of the enol lactone **18b** results in only 35% conversion into the epoxy lactone **19b**. In both epoxy lactones **19a** and **19b**, the epoxidic 4-H is a doublet (*J* 4), whereas in the stereoisomeric epoxy lactone **20a** it shows a slightly broadened singlet.

Several groups have examined the behaviour of cholest-4-en-3-one **21** in the presence of peroxy acids. In the work of Cerny *et al.*[4] MCPBA for 22 h at room temperature gave the two epoxy ketones, 4α,5α- **22** (5%) and 4β,5β-epoxycholestan-3-one **23** (3%), and the enol lactone **24** (4-oxa-4a-homocholest-4a-en-3-one) (9%); *ca.* 30% of the starting material remained unchanged. The low yields reported can be explained by the relatively large amounts of more polar fractions containing transformation products of **22**, **23** and **24**, formed during the attempted separation; these fractions were not investigated.

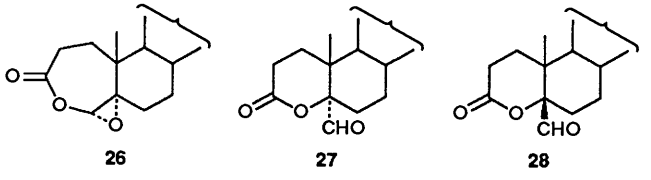
Pinhey and Schaffner,[5] using perbenzoic acid and a small amount of $HClO_4$, isolated only 4α,5α-epoxycholestan-3-one **22**, the enol lactone **24** and several products derived from the

* This and other systematic names used in the paper are according to the 1989 recommendations for the nomenclature of steroids.[10]



21 22 23 24 25

epoxy lactone **25** which was not isolated. A repeat reaction with buffered CF_3CO_3H over 1.5 h at 30–40 °C gave the epoxy ketone **22** (5%), neither the enol lactone **24**, nor the epoxy lactone **25** being obtained. The latter was transformed during the isolation process into the oxa steroid **27** (60%) and products of further oxidation.

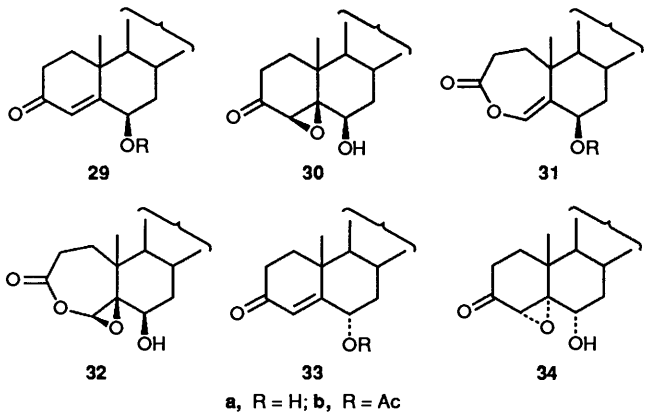


26 27 28

Our results with MCPBA for 2 days at room temperature confirm qualitatively the previous findings. The major Baeyer–Villiger oxidation product was the enol lactone **24** (57%) [δ_H 5.99 (d, *J* 1.25, vinylic 4-H allylically coupled with 6β-H)] accompanied by the stereoisomeric epoxy lactones **25** (4β,5β-epoxy-, 11%) and **26** (4α,5α-epoxy-, 3%), resulting most probably from epoxidation of the enol lactone **24** (see below) [δ_H 4.75 and 4.66 (both s, epoxidic 4-H, respectively]; approximately 28% of the starting material remained unchanged. An additional path leading to the epoxy lactones **25** and **26** might be a Baeyer–Villiger oxidation of the epoxy ketones **22** and **23**; although the latter were not found in the crude reaction mixture, this does not exclude their formation. Indeed, exposure of 4α,5α-epoxycholestan-3-one **22** to MCPBA for 2 days afforded the epoxy lactone **26**, (12%), whilst the stereoisomeric 4β,5β-epoxycholestan-3-one **23** afforded the epoxy lactone **25** (40%). In view of the yields of epoxy lactones obtained in these transformations **22** ⟶ **26**, and **23** ⟶ **25**, as well as the time required to this end, it is reasonable to assume that the major pathway to the formation of epoxy lactones **25** and **26** is epoxidation of the first formed enol lactone **24**.

Indeed, the latter gave the 4α,5α-epoxy lactone **25** (85%) and the 4β,5β-epoxy lactone **26** (15%) in a reaction which proceeded for 20 h only. The yields indicated in these reactions were determined by integration of relevant signals in the NMR spectra of the crude mixtures. Actual yields of isolated products are in these cases misleading, in view of the transformations occurring during chromatography. The results of these and other transformations of enol lactones and epoxy lactones of this kind will be discussed in a forthcoming publication.

The investigation was continued with γ-hydroxy-(acetoxy-)-cholest-4-en-3-ones. Treatment of 6β-hydroxycholest-4-en-3-one **29a** with MCPBA for 5 h, afforded a mixture of the enol lactone **31a** (25%) and the epoxy lactone **32a**, (15%), approximately 50% of the starting material remaining unchanged [δ_H 6.23 (s, vinylic H) and 4.87 (s, epoxidic H, respectively)]. With a reaction time of 20 h, the conversion was 69% and gave the 4β,5β-epoxy ketone **30a** (8%), the enol lactone **31a** (33%) and the 4β,5β-epoxy lactone **32a** (28%). Finally, with a *ca.* 48 h



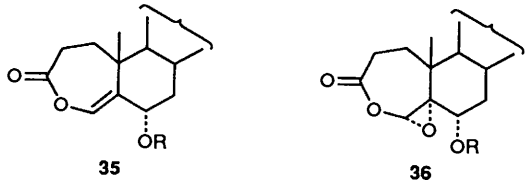
29 30 31 32 33 34

a, R = H; b, R = Ac

reaction time, starting material was entirely consumed, the epoxy ketone **30a** and the enol lactone **31a** having disappeared, only the epoxy lactone **32a** being identifiable (NMR and TLC). In a separate experiment, treatment of the enol lactone **31a** with MCPBA for 16 h resulted in its total conversion into the epoxy lactone **32a**. The latter was also obtained (45%) when the epoxy ketone **30a** was treated with MCPBA, overnight.

Since, from these results, the major source of epoxy lactone **32a** appears to be the enol lactone **31a** and not the epoxy ketone **30a**, clearly the Baeyer–Villiger oxidation leading to the enol lactone **31a** is significantly faster than the epoxidation leading to the epoxy ketone **30a**. The latter was detected in the reaction mixture only when the reaction was allowed to proceed for a longer period of time.

6β-Acetoxycholest-4-en-3-one **29b** upon treatment with MCPBA afforded solely the enol lactone 6β-acetate **31b**, 35% of the starting material remaining unchanged. Hence, acetylation of the 6β-OH group suppressed not only the possibility of epoxidation of the double bond in the enone **29b**, but also that of the double bond in the enol lactone **31b**. 6α-Hydroxycholest-4-en-3-one **33a** afforded, in a 3 h reaction, a mixture of the enol lactone **35a** (30%) and the epoxy lactone **36a** (34%), 36% of the starting material remaining unchanged. With a 22 h reaction the conversion was 85%, the products obtained being the epoxy lactone **36a** (75%) and the epoxy ketone **34** (10%). Compound **33a** upon exposure for the same period of time to a larger excess of MCPBA, was also converted into the epoxy lactone **36**, thus becoming the sole product of this reaction.



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a, R = H; b, R = Ac

From these results, we conclude that the Baeyer–Villiger oxidation of compound **33a** leading to the enol lactone **35a**, is much faster than the epoxidation leading to the epoxy ketone **34**. In view of the transformation of the 4α,5α-epoxy ketone **34** into the epoxy lactone **36a**, the configuration of the epoxy group in the latter is implicitly established as 4α,5α.

The behaviour of 6α-acetoxycholest-4-en-3-one **33b** in the presence of MCPBA is different from that of the 6β-acetoxy stereoisomer **29b**. Whereas the latter (axial acetoxy group) affords only the enol lactone 6β-acetate **31b**, the former (equatorial acetoxy group) is oxidised not only to the enol lactone 6α-acetate **35b**, but also to the corresponding epoxy lactone 6α-acetate **36b**. This finding supports the assumption

that the non-epoxidation of the enol lactone **31b** is due to the steric hindrance of the axial 6β-OAc group. Once this impediment is removed (replacement of 6β-OAc by the equatorial 6α-OAc), the epoxidation to the corresponding epoxy lactone 6α-acetate **36b** takes place. This compound is identical with that prepared by acetylation of **36a**, thus confirming the α-orientation of the 4,5-epoxy group.

Experimental

M.p.s were taken with a Fisher–Johns apparatus and are uncorrected. Column chromatography was performed on silica gel 60, 70–230 mesh (Merck). TLC was carried out on plates of silica gel F_{254} (Merck). Preparative chromatoplates (1 mm thick) were prepared with silica gel PF_{254} (Merck). In chromatography, light petroleum refers to the fraction of b.p. 60–80 °C. Yields are given in mg and/or % of isolated product showing one spot on a chromatoplate; for reactions with difficult separations, or leading to compounds prone to decomposition during the chromatography, yields are based on integration of selected NMR signals. ^{1}H NMR spectra were determined at 80 MHz on a Varian FT-80A spectrometer, at 270 MHz on a Bruker WH and at 400 MHz on a Bruker AMX instrument for solutions in deuteriochloroform containing Me_4Si. J and $W_{\frac{1}{2}}$ values are given in Hz. Mass spectra (electron-impact and/or chemical ionization, as indicated) were obtained by Mrs. M. Chernyak by direct inlet into a Finnigan 4600 quadrupole instrument.

Reactions of Steroidal Ketones with MCPBA

General Procedure.—To a stirred solution of steroidal ketone (0.125 mmol) in dry benzene (8 cm^3), a solution of MCPBA (Fluka, *ca.* 90% purity; 0.137 mmol) in dry benzene (5 cm^3), was added. The reaction was stoped after the indicated time at room temperature (*ca.* 20 °C); the solution was washed twice with aq. ammonia (5%) and once with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure (water bath, below 40 °C). The crude mixture was prepared by chromatography (column or preparative plates, as indicated).

Reaction of 3β-*Hydroxycholest-4-en-6-one* **5a**[6,11] *with MCPBA.*—The ketone **5a** (130 mg) and MCPBA (70 mg); time 48 h; column chromatography (light petroleum–ethyl acetate 9:1) afforded 3β-hydroxy-6-oxa-7a-homocholest-4-en-7-one **7a** (60 mg), m.p. 119–121 °C (MeOH); δ_H 0.68 (s, 18-H_3), 1.01 (s, 19-H_3), 4.3 (m, $W_{\frac{1}{2}}$ 10, 3α-H) and 5.53 (d, J 4, 4-H); m/z (EI, 30 eV) 417 (M^+ + 1, 55%), 416 (M^+, 15), 399 (M^+ − 17, 95) and 388 (M^+ − 28, 58); m/z (CI) 417 (M^+ + 1, 100%) and 399 (M^+ + 1-H_2O, 79) (Found: C, 77.4; H, 10.7. $C_{27}H_{44}O_3$ requires C, 77.8; H, 10.65%). Elution with light petroleum–ethyl acetate (8:2) afforded 4β,5β-epoxy-3β-hydroxycholestan-6-one[7] **6a** (35 mg), identified by comparison (NMR and TLC) with an authentic sample. The presence of 4β,5-epoxy-3β-hydroxy-6-oxa-7a-homo-5β-cholestan-7-one **8** in the crude reaction mixture was detected by TLC and NMR (*ca.* 5% by integration of the 4α-H signal). Compound **8** is decomposed during this chromatography.

Reaction of the Cholestanone **6a** *with MCPBA.*—Compound **6a** was prepared from the cholestenone **5a** by treatment with H_2O_2/OH^- according to ref. 7, **6a** (30 mg), MCPBA (20 mg); time, 20 h. Purification on a chromatoplate (toluene–ethyl acetate, 2:1). Upper band, the cholestanone **8** (20 mg), m.p. 148–150 °C (acetone–hexane); δ_H 0.69 (s, 18-H_3), 1.11 (s, 19-H_3), 3.63 (d, J 3, 4α-H) and 4.1 (m, br, 3α-H); m/z (EI, 30 eV) 432 (M^+, 8%) and 414 (M^+ − H_2O, 8); m/z (CI) 433 (M^+ + 1, 100%) and 415 (M^+ 1-H_2O, 62) (Found: C, 75.2; H, 10.1; $C_{27}H_{44}O_4$ requires C, 74.95; H, 10.25%). Lower band, unchanged compound **6a** (8 mg).

Reaction of the Cholestenone **7a** *with MCPBA.*—**7a** (20 mg), MCPBA (10 mg); time 20 h. The NMR spectrum of the crude mixture indicated the presence of a *ca.* 1:1 mixture of **8** and 4α,5-epoxy-3β-hydroxy-6-oxa-7a-homo-5α-cholestan-7-one **9**. Separation was achieved on a chromatoplate (toluene–ethyl acetate, 5:1). Upper band, compound **9a**; it could not be crystallised; δ_H 0.69 (s, 18-H_3), 1.17 (s, 19-H_3), 3.36 (s, slightly broadened, 4β-H) and 4.0 (m, broad, 3α-H). Lower band (*ca.* 10 mg), inseparable mixture of enol lactone **7a** and epoxy lactone **8**.

Reaction of the epoxy lactone **8** *with base.* To a solution of compound **8** (20 mg) in methanol (8 cm^3), methanolic NaOH (5%; 2 cm^3) was added. After 2 h at room temp., the solution was neutralised with dilute HCl and evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution washed with water, dried (Na_2SO_4), and evaporated. The residue was purified on a chromatoplate (toluene–ethyl acetate, 2:1). Major band: methyl 3,4-dihydroxy-5-oxo-5,6-secocholestan-6-oate **10a** (8 mg); δ_H 0.67 (s, 18-H_3), 1.09 (s, 19-H_3), 3.59 (s, CO_2Me), 3.94 (OH), 4.35 (m, $W_{\frac{1}{2}}$ 10, 3-H) and 4.76 (d, J 4.5, 4-H); m/z (EI, 50 eV) 465 (M^+ + 1, 20) and 464 (M^+, 28). Acetylation of the product **10a** with acetic anhydride and pyridine afforded the diacetate **10b**; although homogeneous on TLC, it could not be crystallised; δ_H 0.67 (s, 18-H_3), 1.09 (s, 19-H_3), 1.99 (s, CO_2Me), 2.02 (s, CO_2Me), 3.56 (s, COMe), 5.64 (m, $W_{\frac{1}{2}}$ 9, 3α-H) and 5.83 (d, J 4.5, 4α-H).

Reaction of 3β-*Acetoxycholest-4-en-6-one* **5b**[6,11] *with MCPBA.*—The ketone **5b** (300 mg), MCPBA (150 mg); time 36 h. Separation by column chromatography, (light petroleum–ethyl acetate, 95:5) gave unchanged starting material (100 mg). Further elution gave 3β-acetoxy-6-oxa-7a-homocholest-4-en-7-one **7b** (140 mg), homogeneous on TLC; it could not be crystallised; δ_H(400 MHz) 0.69 (s, 18-H_3), 1.05 (s, 19-H_3), 2.05 (s, CO_2Me), 5.33 (t, J 4, 3α-H) and 5.50 (d, J 4, 4-H); m/z (EI, 30 eV) 458 (M^+, 38%) and 399 (M^+ − 59, 100). Elution with light petroleum–ethyl acetate (9:1) gave 3β-acetoxy-4β,5β-epoxycholestan-6-one **6b** (10 mg), m.p. 101–103 °C (MeOH) (lit.,[7] 102–103 °C). Elution with ethyl acetate gave a polar mixture (29 mg) of decomposition products of the enol lactone **7b**.

*Decomposition of the Enol Lactone-*3β-*acetate* **7b** *by Prolonged Contact with Silica Gel.*—A solution of compound **7b** (50 mg) in light petroleum–ethyl acetate (9:1; 10 cm^3) was adsorbed onto silica gel (70–230 mesh, 10 g). After 20 h, elution with light petroleum–ethyl acetate (1:1) afforded unchanged compound **7b** (8 mg). Elution with ethyl acetate gave 5-oxo-5,6-secocholest-3-en-6-oic acid **12** (30 mg), homogeneous on TLC; δ_H 0.66 (s, 18-H_3), 1.08 (s, 19-H_3), 5.86 (d, J 10, 4-H) and 6.7 (m, $W_{\frac{1}{2}}$ 16, 3-H); ν_{max}($CHCl_3$)/cm^{-1} 1708 and 1670; λ_{max}(EtOH)/nm 228 (ε 9100); m/z (EI 50 eV) 417 (M^+ + 1, 88%), 416 (M^+, 100%) and 399 (M^+ − 17, 70). Further elution with ethyl acetate gave 3β-acetoxy-5-oxo-5,6-secocholestan-6-oic acid **11** (*ca.* 5 mg), m.p. 129–131 °C (MeOH); δ_H(270 MHz) 0.69 (s, 18-H_3), 1.05 (s, 19-H_3), 2.01 (s, CO_2Me) 2.43 (d, J 14.5, 4-H_A), 3.21 (dd, J 14.5, 4.3, 4-H_B) and 5.38 (m, $W_{\frac{1}{2}}$ 10, 3α-H); ν_{max}($CHCl_3$)/cm^{-1} 1731 and 1706; m/z (EI, 50 eV) 461 (M^+ − Me, 62%), 416 (M^+ − 60, 11) and 372 (M^+ − AcOH − CO_2, 65).

Treatment of the Cholestenone **7b** *with Methanolic* NaOH.—To a stirred solution of compound **7b** (65 mg) in methanol (10 cm^3), methanolic NaOH (5%, 1 cm^3) was added. After 90 min, the solution was neutralised with dilute HCl (1:4) and the solvent was removed under reduced pressure. The crude mix-

ture was separated on a chromatoplate (toluene–ethyl acetate, 5:1). Upper band, methyl 5-oxo-5,6-secocholest-3-en-6-oate **13** (25 mg), homogeneous on TLC; δ_H 0.66 (s, 18-H_3), 1.09 (s, 19-H_3), 3.57 (s, CO_2Me), 5.79 (d, *J* 10, 4-H) and 6.7 (m, $W_{\frac{1}{2}}$ 16, 3-H); λ_{max}(EtOH)/nm 231 (ε 8740); *m/z* (EI, 50 eV) 430 (M^+, 85%), 399 (M^+ − OMe), 38) and 357 (M^+ − CH_2CO_2-Me, 100). Lower band, methyl 3-methoxy-5-oxo-5,6-secocholestan-6-oate **14** (14 mg); δ_H 0.66 (s, 18-H_3), 1.01 (s, 19-H_3), 3.10 (dd, *J* 14, 4, 4-H) and 3.8 (m, $W_{\frac{1}{2}}$ 9, 3-H); *m/z* (EI, 50 eV) 463 (M^+ + 1, 65%), 431 (M^+ − OMe, 30) and 389 (M^+ − CO_2Me, 52). The same mixture of compounds **13** and **14** was obtained by heating to reflux for 3 h, a solution of compound **12** (30 mg) in methanol (10 cm^3) containing a trace of toluene-*p*-sulfonic acid.

Epoxidation of 3α-*Hydroxycholest*-4-*en*-6-*one* **15a**[6] *with Alkaline* H_2O_2.—To an ice cold stirred solution of compound **15a** (50 mg) in methanol (8 cm^3), cold methanolic KOH (5%; 0.5 cm^3) was added. Stirring was continued for 30 min at the same temperature, followed by 20 min at room temp. The product was extracted with ethyl acetate and the extract was washed with saturated brine, dried (Na_2SO_4) and evaporated. The product was purified on a chromatoplate (toluene–ethyl acetate, 2:1): major band, 4β,5β-epoxy-3α-hydroxycholestan-6-one **17a** (20 mg), m.p. 186–188 °C (MeOH); δ_H 0.66 (s, 18-H_3), 1.00 (s, 19-H_3), 2.98 (m, $W_{\frac{1}{2}}$ 2.5, 4α-H) and 4.01 (t, *J* 7.5, 3β-H); *m/z* (EI, 50 eV) 416 (M^+, 100%) and 398 (M^+ − H_2O, 70) (Found: C, 77.9; H, 10.5. $C_{27}H_{44}O_3$ requires C, 77.8; H, 10.65%).

Reaction of 3α-*Hydroxycholest*-4-*en*-6-*one* **15a** *with MCPBA*.—Compound **15a** (30 mg), MCPBA (15 mg); time 20 h. Separation on a chromatoplate (toluene–ethyl acetate, 5:1). Upper band, 4α,5α-epoxy-3α-hydroxycholestan-6-one **16** (10 mg), identical with the product obtained[6] by treatment of the title compound **15a** with Sharpless reagent. Middle band, unchanged compound **15a** (*ca.* 5 mg). Lower band, the cholestanone **17a** (~5 mg), identical with the product obtained by treatment of compound **15a** with H_2O_2/OH^-. The ratio between compounds **15a**, **16** and **17** before fractionation was *ca.* 45:25:25 (NMR evidence). When the treatment of compound **15a** (40 mg) with MCPBA (20 mg) was repeated for a longer period of time (48 h), an inseparable mixture of the enol lactone **18a**, accompanied by the epoxy lactones **19a** and **20a** was obtained. The NMR signals of 4-H in this mixture were: **18a**, δ_H 5.45 (d, *J* 3); **19a**, 3.60 (d, *J* 4); and **20**, 3.38 (s, slightly broadened). Acetylation of the above mixture (with acetic anhydride and pyridine) afforded a mixture of acetates from which only 3α-acetoxy-6-oxa-7a-homocholest-4-en-7-one **18b** could be separated in almost pure state (chromatoplate). It was identical (TLC and NMR) with the compound obtained by treatment of compound **15b** with MCPBA.

Reaction of 3α-*Acetoxycholest*-4-*en*-6-*one* **15b**[6] *with MCPBA*.—Compound **15b** (40 mg), MCPBA (20 mg); time 36 h. Separation on a chromatoplate (toluene–ethyl acetate, 9:1). Upper band, the cholestenone **18b** (20 mg), m.p. 120–121 °C (MeOH); δ_H 0.68 (18-H_3), 0.98 (s, 19-H_3), 2.04 (s, CO_2Me), 5.3 (overlap of 3β-H and 4-H signals); *m/z* (EI, 30 eV) 458 (M^+, 69%) and 399 (M^+ − 59, 100) (Found: C, 76.0; H, 10.05; $C_{29}H_{46}O_4$ requires C, 75.9; H, 10.1%). Lower band, unchanged compound **15b** (*ca.* 7 mg).

Reaction of the Cholestanone **17a** *with MCPBA*.—**17a** (10 mg), MCPBA (5 mg); time, 20 h; chromatoplate (toluene–ethyl acetate, 2:1). Upper band, 4β,5-epoxy-3α-hydroxy-6-oxa-7a-homo-5β-cholestan-7-one **20a** (4 mg), which could not be crystallised; δ_H 0.71 (s, 18-H_3), 1.11 (s, 19-H_3), 3.38 (s, slightly broadened, 4α-H), 4.17 (m, br, 3β-H); *m/z* (CI) 433 (M^+ + 1, 60%) and 415 (M^+ + 1-H_2O, 100). Lower band, unchanged compound **17a**.

Reaction of Cholest-4-*en*-3-*one* **21** *with MCPBA*.—Compound **21** (500 mg in benzene, 20 cm^3), MCPBA (200 mg in benzene, 15 cm^3); time, 36 h. Column chromatography (light petroleum–ethyl acetate, 98:2) gave 4-oxa-4a-homocholest-4a-en-3-one **24** (200 mg), m.p. 82–84 °C (MeOH) [lit.,[5] 70–72 °C (MeOH), lit.,[4] 83–84 °C (light petroleum)]; δ_H 0.66 (s, 18-H_3), 1.08 (s, 19-H_3) and 5.99 (d, *J* 1.25, 4-H). Elution with light petroleum–ethyl acetate (95:5) gave 4aβ,5-epoxy-4-oxa-4a-homo-5β-cholestan-3-one **25** (30 mg), m.p. 100–102 °C (MeOH); δ_H 0.67 (s, 18-H_3), 1.16 (s, 19-H_3) and 4.75 (s, 4α-H); *m/z* (EI, 70 eV) 417 (M^+ + 1, 25%), 416 (M^+, 11), 399 (M^+ + 1 − H_2O, 35) and 387 (M^+ − CHO, 100) (Found: C, 77.6; H, 10.5. $C_{27}H_{44}O_3$ requires C, 77.8; H, 10.65%). Further elution gave unchanged compound **21** (130 mg). Elution with ethyl acetate gave polar fractions. Although 4aα,5-epoxy-4-oxa-4a-homo-5α-cholestan-3-one **26** was detected in the crude reaction mixture [δ_H 4.66 (4β-H)], it could not be isolated from the chromatographic column.

Reaction of 4β,5β-*Epoxycholestan*-3-*one* **23** *with MCPBA*.—Compound **23** was obtained according to ref. 13. The ketone **23** (200 mg), MCPBA (100 mg); time, 2 days. The crude product contained only unchanged epoxy ketone **23** and epoxy lactone **25** [conversion 40% (NMR)]. Separation was achieved by column chromatography. Elution with light petroleum–ethyl acetate (95:5) gave starting material **23** (85 mg), followed by the cholestanone **25** (50 mg), identical (TLC and NMR) with the compound obtained by treatment of compound **21** with MCPBA. Elution with light petroleum–ethyl acetate (9:1) gave 5α-formyl-4-oxacholestan-3-one **27** (25 mg), m.p. 128–130 °C (MeOH) (lit.,[5] 128–131 °C); δ_H 0.69 (s, 18-H_3), 1.07 (s, 19-H_3) and 10.4 (s, CHO). In ref. 5 the CHO signal is at δ_H 9.1.

Reaction of 4α,5α-*Epoxycholestan*-3-*one* **22** *with MCPBA*.—Compound **22** was prepared from 3β-*acetoxycholest*-4-*ene* according to ref. 8. Compound **22** (100 mg), MCPBA (60 mg); time, 2 days. The crude product contained only unchanged epoxy ketone **22** and epoxy lactone **26** [conversion 12% (NMR)]. Separation was achieved by column chromatography. Elution with light petroleum–ethyl acetate (98:2) gave unchanged material (70 mg). Further elution gave the cholestanone **26** (8 mg), m.p. 131–132 °C (MeOH); δ_H 0.67 (s, 18-H_3), 1.14 (s, 19-H_3) and 4.66 (s, 4β-H). Elution with light petroleum–ethyl acetate (9:1) gave 5-formyl-4-oxa-5β-cholestan-3-one **28** (5 mg), m.p. 146–148 °C (MeOH) (lit.,[5] m.p. 145 °C); δ_H 0.69 (s, 18-H_3), 1.11 (s, 19-H_3) and 9.68 (s, CHO).

Reaction of 6β-*Hydroxycholest*-4-*en*-3-*one* **29a**[6,12] *with MCPBA*.—(a) Compound **29a** (50 mg), MCPBA (30 mg); time 5 h. Separation was achieved on a chromatoplate (toluene–ethyl acetate, 5:1). Upper band, 4aβ,5-epoxy-6β-hydroxy-4-oxa-4a-homo-5β-cholestan-3-one **32** (5 mg), m.p. 171–173 °C (MeOH); δ_H 0.70 (s, 18-H_3), 1.30 (s, 19-H_3), 3.33 (m, $W_{\frac{1}{2}}$ 7.5, 6α-H) and 4.87 (s, 4α-H); *m/z* (EI, 30 eV) 432 (M^+, 7%) and 414 (M^+ − H_2O, 32) (Found: C, 74.8; H, 10.15. $C_{27}H_{44}O_4$ requires C, 74.95; H, 10.25%). Middle band, 6β-hydroxy-4-oxa-4a-homocholest-4a-en-3-one **31a** (10 mg), m.p. 158–160 °C (MeOH); δ_H 0.70 (s, 18-H_3), 1.28 (s, 19-H_3), 4.22 (m, $W_{\frac{1}{2}}$ 7.5, 6α-H) and 6.23 (s, 4-H); *m/z* (EI, 30 eV) 416 (M^+, 10%), 399 (M^+ − 17, 25) and 398 (M^+ − H_2O, 23) (Found: C, 77.9; H, 10.5. $C_{27}H_{44}O_3$ requires C, 77.8; H, 10.65%). Lower band, unchanged starting material (25 mg).

(b) Quantities as above; time, 20 h. Four bands were separated. Upper band, **30a**[6,14] (4 mg); 2nd band, **32** (10 mg); 3rd band, **31a** (12 mg); 4th band, **29a** (15 mg).

(c) Quantities as above: time, 48 h. The crude product contained only compound **32a** (NMR and TLC). After chromatography, 30 mg was isolated (partial decomposition).

Reaction of 4β,5β-*Epoxy*-6β-*hydroxycholestan*-3-*one* **30a** *with MCPBA*.—This compound was prepared according to refs. 6 and 14. **30a** (40 mg), MCPBA (20 mg); time, 20 h. Chromatoplate (toluene–ethyl acetate, 5:1). Upper band, unchanged **30a** (20 mg). Lower band, epoxy-lactone **32a** (18 mg).

Reaction of 6β-*Hydroxy-enol Lactone* **31a** *with MCPBA*.—Compound **31a** (20 mg), MCPBA (10 mg); time, 16 h. The crude product contained only 6β-hydroxy-epoxy lactone **32a** (NMR and TLC). Purification on a chromatoplate (toluene–ethyl acetate, 5:1) afforded the pure compound (10 mg), identical with that obtained from compound **29a**.

Reaction of 6β-*Acetoxycholest*-4-*en*-3-*one* **29b**[12] *with MCPBA*.—Compound **29b** (40 mg), MCPBA (30 mg); time, 20 h. Separation was achieved on a chromatoplate (toluene–ethyl acetate, 9:1). Upper band, 6β-acetoxy-4-oxa-4a-homocholest-4a-en-3-one **31b** (10 mg), homogeneous on TLC; δ 0.71 (s, 18-H_3), 1.17 (s, 19-H_3), 2.02 (s, CO_2Me), 5.27 (m, $W_{\frac{1}{2}}$ 7.5, 6α-H) and 6.39 (s, 4-H). Lower band, unchanged material, 12 mg.

Reaction of 6α-*Hydroxycholest*-4-*en*-3-*one* **33a**[6,15] *with MCPBA*.—(a) Compound **33a** (40 mg), MCPBA (20 mg); time, 3 h. Separation was achieved on a chromatoplate (toluene–ethyl acetate, 3:1). Upper band, 4aα,5-epoxy-6α-hydroxy-4-oxa-4a-homo-5α-cholestan-3-one **36a** (10 mg), m.p. 120–121 °C (MeOH); δ_H 0.67 (s, 18-H_3), 1.14 (s, 19-H_3), 3.93 (dd, *J* 12, 5, 6β-H); *m/z* (EI, 30 eV) 433 ($M^+ + 1$, 8%), 414 ($M^+ - H_2O$, 10%) and 403 ($M^+ - CHO$, 83); *m/z* (CI) 433 ($M^+ + 1$, 100%) and 415 ($M^+ + 1\text{-}H_2O$, 85%). Middle band, 6α-hydroxy-4-oxa-4a-homocholest-4a-en-3-one **35a** (8 mg), homogeneous on TLC; δ_H 0.68 (s, 18-H_3), 1.08 (s, 19-H_3), 4.36 (ddd, *J* 11.5, 4, 1.25, 6β-H) and 6.40 (d, *J* 1.25, 4-H). Lower band, unchanged compound **33a** (12 mg).

(b) Quantities as above; time, 22 h. Upper band, 4α,5α-epoxy-6α-hydroxycholestan-3-one **34** (4 mg), identical with an authentic sample;[6] 2nd band, **36a** (25 mg); 3rd band, unchanged **33a** (5 mg).

(c) **33a** (30 mg), MCPBA (30 mg); time 22 h. The crude product contained only the epoxy lactone **36a** (NMR and TLC). Only 17 mg was isolated after chromatography (partial decomposition). Acetylation of compound **36a** with acetic anhydride and pyridine gave the epoxy lactone 6α-acetate **36b**, identical with that obtained by oxidation with MCPBA of compound **33b**. Acetylation of compound **35a** gave the enol lactone 6α-acetate **35b** identical with that obtained by direct oxidation of **33b**.

Reaction of 6α-*Acetoxycholest*-4-*en*-3-*one* **33b**[15] *with MCPBA*. Compound **33b** (30 mg), MCPBA (15 mg); time 20 h. Separation was achieved on a chromatoplate (toluene–ethyl acetate, 10:1). Upper band, 6α-acetoxy-4aα,5-epoxy-4-oxa-4a-homo-5α-cholestan-3-one **36b**, m.p. 111–112 °C (MeOH); δ_H 0.69 (s, 18-H_3), 1.21 (s, 19-H_3), 1.99 (s, CO_2Me), 5.13 (dd, *J* 12, 5, 6β-H) and 5.20 (s, 4β-H); *m/z* (EI, 50 eV) 475 ($M^+ + 1$, 18%), 445 ($M^+ - CHO$, 63) and 414 ($M^+ - 60$, 100). Middle band, 6α-acetoxy-4-oxa-4a-homocholest-4a-en-3-one **35b** (10 mg), m.p. 80–82 °C (MeOH–H_2O); δ_H 0.68 (s, 18-H_3), 1.15 (s, 19-H_3), 2.09 (s, CO_2Me), 5.44 (ddd, *J* 11.5, 4, 1.25, 6β-H) and 6.16 (d, *J* 1.25, 4-H); *m/z* (EI, 50 eV) 458 (M^+, 15%) and 399 ($M^+ - 59$, 100). Lower band, unchanged compound **33b** (8 mg).

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