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STUDIES ON EPOXIDES—VI[1]

OPENING REACTIONS OF α-SUBSTITUTED EPOXYSTEROIDS

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Abstract—Treatment of 1,2-epoxy-3-ketosteroids with tosylhydrazine and sodium borohydride in methanol lead to mixtures consisting of (i) ring A seco-acetylenic alcohols, (ii) methoxyhydrins formed by opening of the epoxide ring following the carbonyl reduction, and (iii) an epoxy-3,3-dimethylketal. For the corresponding 4-methylene derivative, the ring A fragmentation product was found to be the conjugated en-yne **8a**. Reduction of these epoxyketones with sodium borohydride alone affords mixtures of *cis*- and *trans* epoxyalcohols; the *cis* derivatives were unaffected by heating with sodium borohydride in methanol, whereas the *trans* were converted into the corresponding diaxial methoxyhydrins.

The observation that steroidal 1,4-diketones are more stable in the A/B *cis* rather than the *trans* series[2] prompted us to investigate the synthesis of such systems to study their equilibration conditions.[3] One of the early synthetic schemes started with the 4-methylene derivatives of 1,2-epoxy-3-ketosteroids;[4] these were expected to lead, by reduction of the 3-one and oxidative cleavage of the exocyclic double bond, to 1-hydroxy-4-ketosteroids. Although this sequence did not give the expected results, we wish to present certain aspects of this work.

Direct methylenation of 1α,2α-epoxy-5α-cholestan-3-one[5] (**1**) according to the procedure developed in the androstane series[4] afforded the corresponding 4-methylene derivative (**2**). Similarly, 1β,2β-epoxy-5α[6]- and 1β,2β-epoxy-5β-cholestan-3-one[3] yielded the 4-methylene derivatives **3** and **4**, respectively. Whereas **2** crystallised from the reaction in high yield, chromatographic separation was needed for the purification of **3** and **4**. The characterisation of these compounds (**2–4**) is based mainly on UV, NMR and mass spectra data.

The experiments to remove the 3-oxo group were performed on **2**, the most readily available isomer. The mixed hydride procedure (LAH-$AlCl_3$)[7] successfully used for the reduction of carbonyl to methylene in other steroidal ketones[8] was attempted. Treatment of **2** with this reagent in refluxing ether afforded only diol **5a**, also obtained when LAH alone was used.

The configurational assignments of **5a** are based on its NMR spectrum which shows a triplet at δ 3·81 for the 1βH and a broad multiplet at δ 4·39 for the axial 3αH; as expected the signals of the exocyclic methylene protons which are at δ 6·28 and 5·30 in the starting ketone **2** are shifted upfield becoming narrow multiplets at δ 5·07 and 4·67. In the corresponding acetate **5b** the signal of the 1βH and 3αH are at δ 4·96 and 5·42.

$NaBH_4$ reduction at room temp of **2** left the epoxide ring unchanged whereas the carbonyl group was stereoselectivity reduced to the 3β-ol **6a** (narrow-triplet at δ 4·38 for the adjacent 3αH; δ 5·50 for this proton in the acetate **6b**). The dihedral angle formed by the 3αH and the epoxidic 2βH in **6** is ~90°, and therefore the signal of the former is split only by the terminal methylene protons; this observation is supported by the narrow band at δ 3·13 of the almost equivalent epoxidic protons, no significant splitting by the 3αH being observed. It is interesting to note that stereoselective hydride reduction of the carbonyl group in **2** to the equatorial 3β-ol is in contrast with

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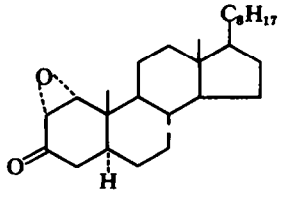

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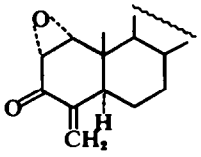

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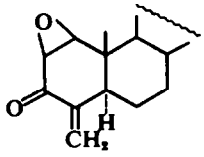

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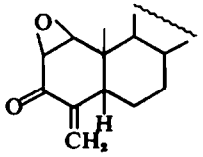

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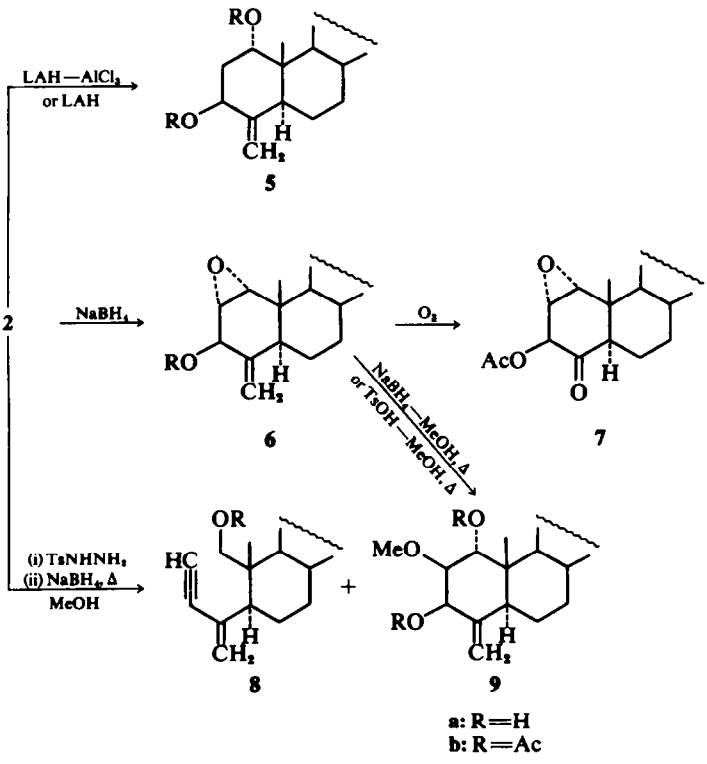


the $NaBH_4$ reduction in a related endocyclic conjugated epoxyketone (17β-acetoxy-1α,2α-epoxyandrost-4-en-3-one) which gives the 3α-ol derivative.[9]

Ozonolysis of the double bond in **6b** afforded 1α,2α-epoxy-3β-acetoxy-5α-cholestan-4-one (**7**) in which the configurational assignment of the 3-acetate group is unequivocal: the two equivalent epoxidic protons and the 3H give singlets at δ 3·29 and 5·33 Hz respectively, confirming the α orientation of the proton adjacent to the acetate group.

Since the LAH-$AlCl_3$ treatment of **2** failed to give a 3-desoxo derivative, an alternative path was attempted, based on the reported[10] borohydride reduction of unsubstituted tosylhydrazones (at the time, the fragmentation of $\alpha\beta$-epoxyketones with tosylhydrazine[11,12] was not yet published). In our case **2** in MeOH with 1·1 moles of tosylhydrazine, followed by addition of $NaBH_4$ and heating, afforded two compounds identified as **8a** and **9a**. The ene-yne structure assigned to **8a** (1-hydroxy-4-methylene-1,2-seco-5α-cholest-2-yne) is based on its mode of formation as rationalised for saturated epoxyketones,[11,12] attention being paid to the fact that the C_1 aldehyde formed in the initial step of the reaction, was subsequently reduced by the borohydride anion to a primary alcohol. This structure is supported by spectral analysis, IR: ν_{max} 3300 cm^{-1} for an acetylenic bond, UV: λ_{max} 223 nm (ϵ 9700) and the NMR data: a signal for an acetylenic proton at δ 2·96,[13] two narrow multiplets for the terminal methylene protons at δ 5·61 and 5·37 and a two protons singlet at δ 3·44 for the C_1 protons; these two protons become non-equivalent in the acetate **8b** (AB pattern, J 12 Hz), most probably due to the bulky acetate group restricting the rotation about the C_1-C_{10} bond. The structure assigned to **9a** (1α,3β-dihydroxy-2β-methoxy-4-methylene-5α-cholestane) is based on its NMR spectrum displaying a doublet at δ 3·96 (J 3·5 Hz) for 1βH, multiplets at δ 3·63 and 4·31 for 2α- and 3αH respectively, as well as narrow multiplets for the terminal methylene protons at δ 5·13 and 4·76. This structure was also confirmed by acid catalysed opening in MeOH of the epoxide in **6**, leading to the same compound **9**.

In order to explain the formation of **9** together with **8**, two alternatives can be advanced. First, toluene-p-sulphinic acid which is formed during the fragmentation reaction leading to **8**[11,12] could act as catalyst for the opening of the epoxide ring in the unreacted starting epoxyketone **2**.

The second explanation is that part of the epoxyketone which did not react with tosylhydrazine was attacked by borohydride in MeOH reducing first the 3-one to the 3β-ol, and then opening the epoxide ring. Since no methoxyl containing compound could be detected in the crude product obtained in the first step of the reaction (before $NaBH_4$ treatment), the former explanation seems

less plausible than the latter. Indeed, heating of **6a** with $NaBH_4$ alone in MeOH induced its partial conversion into **9a**.

To investigate this reaction further, the saturated epoxyketone **1** was treated with tosylhydrazine followed by $NaBH_4$, using the same conditions as described for **2**. In this case three compounds were isolated by chromatography of the crude product: the fragmentation derivative **10**, the epoxydimethylketal **11** and the 1α,3β-dihydroxy-2β-methoxy derivative (**12**).

The structure of **10** is based on its NMR spectrum; it is noteworthy that in contrast to the acetate **8b**, the C_1 protons are equivalent in the acetate **10b**. Inspection of models shows that in **10b** the acetate group can rotate freely about the C_1-C_{10} bond. As expected, compound **10a** has also been obtained by fragmentation of the isomeric 1β,2β-epoxy-3-ketone.[6]

The structure assigned to **11** is supported by two MeO signals in its NMR spectrum as well as by its hydrolysis to starting epoxyketone **1**. The formation of **11** exemplifies the easy ketalisation of 3-ketosteroids by MeOH under acid catalysis,[14] the toluene *p*-sulphinic acid formed during the fragmentation reaction probably being the catalyst. Also worthy of mention is the reaction of pyridinium 17-yl- and/or -20-yl sulphate-3-oxo-steroids with $NaBH_4$ in MeOH, when ketalisation of the 3-keto group, instead of the expected reduction, takes place due to the acidity of the pyridinium ion.[15] The structure assigned to **12** is confirmed by its independent preparation from 1α,2α-epoxy-3β-hydroxy-5α-cholestane (**14a**).

Treatment of **1** with $NaBH_4$ in MeOH at room temp afforded a mixture (4:6) of the isomeric epoxyalcohols **13a** and **14a** which could be separated by chromatography.* The configurational assignments in compounds **13** and **14** were supported by the NMR signals of the 3-H: narrow multiplet (W1/2 10 Hz) at δ 4·07 for **13a** and broad multiplet (W1/2 18 Hz) at δ 4·03 for **14a**. In addition, the NMR spectra of **14a** and **b** display the characteristic narrow bands for epoxidic 1-H and 2-H, as encountered in the corresponding derivatives **6** and **7**. The characterisation was also performed on the two acetates **13b** and **14b**; the latter has been prepared by another route.[6]

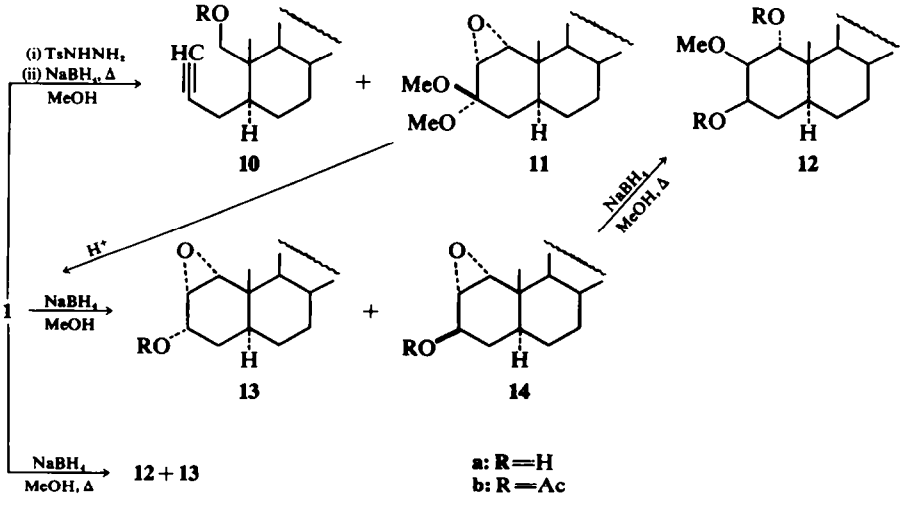
The same reaction at reflux afforded a mixture (6:4) of **12a** and **13a**. Heating *trans* epoxyalcohol **14a** with $NaBH_4$ in MeOH produced quantitatively **12a**, whereas the *cis* epoxyalcohol **13a** remained unchanged even after prolonged heating, thus explaining the formation of the two components from **1** under the heating conditions.

In the cases of the *trans* epoxyalcohols, **6** and **14**, the opening of the 1α,2α-epoxide is diaxial producing **9** and **12** respectively. To our knowledge methoxyhydrin formation by $NaBH_4$-MeOH treatment of an epoxide has only been encountered in certain epoxyalcohols of the inositol series, in which the products have been assigned a diequatorial orientation.[17]

The scope and limitations of this interesting reaction involving nucleophilic attack by MeOH in the presence of $NaBH_4$ are being now investigated on various substituted epoxides. So far, from our preliminary results only *trans* epoxyalcohols would undergo such a reaction, whereas *cis* epoxyalcohols or epoxides without a vicinal hydroxyl group remain unaffected.

When 1β,2β-epoxy-5β-cholestan-3-one[3] and its exocyclic methylene derivative **4** were subjected to fragmentation, no clean compounds could be isolated, although the NMR spectra of the crude products indicated that fragmentation did take

*Similar reductions in the androstane series afforded the 3β-alcohol in 60% yield, without isolation of the 3α-isomer.[16a,b]



place as indicated by the presence of an aldehydic proton signal.

The formation of the en-yne **8a** from **2** prompted us to investigate this reaction with endocyclic α,β-unsaturated epoxyketones. Thus, 1α,2α-epoxycholest-4-en-3-one,[18] 1α,2α-epoxycholesta-4,6-dien-3-one[3] and 4β,5β-epoxycholest-1-en-3-one[19] were submitted to the same fragmentation conditions, but no clean products could be isolated even after careful chromatography.

EXPERIMENTAL

M.ps were determined with Fisher-Johns apparatus and are uncorrected. Optical rotations were recorded with an automatic Perkin-Elmer 141 polarimeter and refer to $CHCl_3$ solns. UV spectra were recorded on a Cary 14 spectrophotometer with EtOH solns. A Perkin-Elmer Infracord 137 with $CHCl_3$ solns (IR) and a Varian A-60 spectrometer with $CDCl_3$ solns (NMR) were employed. Microanalyses were carried out in our Institute under the direction of Mr. R. Heller. MW's were determined with an Atlas CH4 mass spectrometer. TLC was done on chromatoplates of silicagel G (Merck) and spots were developed with I_2 vapour. Neutral Woelm alumina activity III and Merck silicagel were used for chromatography.

1α,2α-Epoxy-4-methylene-5α-cholestan-3-one (**2**). An ethanolic (120 ml) soln of 1α,2α-epoxy-5α-cholestan-3-one (**1**)[5] (3·0 g) containing aq. formaldehyde 336–38%, 12 ml) and aq AcONa (1·8 g in 8 ml H_2O) was heated to reflux for 5 h, cooled and neutralised with AcOH. The crystalline separated product (2·3 g, 74%) was used for subsequent reactions. Pure **2** crystallised from MeOH, m.p. 121–123°, $[\alpha]_D$ + 113° (*c*, 1·0), λ_{max} 234 nm (ϵ 5600); ν_{max} 1686 and 1607 cm^{-1}; NMR: δ 6·28 and 5·30 (4-CH_2, two m), 3·61 (1-H, d, *J* 4 Hz), 3·39 (2-H, d, *J* 4 Hz), 0·80 (19-H, s) and 0·69 (18-H, s). (Found: C, 81·77; H, 10·66; M^+ 412; $C_{28}H_{44}O_2$ requires: C, 81·50; H, 10·75%; M.W. 412·6).

1β,2β-Epoxy-4-methylene-5α-cholestan-3-one (**3**). A soln of 1β,2β-epoxy-5α-cholestan-3-one[6] (150 mg) in EtOH (6 ml) containing aq. fomaldehyde (0·8 ml) and aq AcONa (90 mg in 0·5 ml H_2O) was heated to reflux for 64 h, cooled, neutralised with AcOH, evaporated to a small volume, diluted with H_2O and Et_2O extracted. The ethereal soln was H_2O washed, dried, evaporated and the residue chromatographed on alumina; elution with hexane-ether 9:1 gave **3** (30 mg, 19%), m.p. 175–177° (CH_2Cl_2-MeOH), $[\alpha]_D$ + 61·5° (*c*, 0·43); λ_{max} 225 nm (e 2500); ν_{max} 1700 and 1617 cm^{-1}; NMR: δ 6·03 and 5·13 (4-CH_2, two m), 3·48 (1-H, d, *J* 4 Hz), 3·21 (2-H, d, *J* 4 Hz), 0·83 (19-H, s) and 0·72 (18-H, s). (Found: M^+ 412; $C_{28}H_{44}O_2$ requires: M.W. 412·6).

1β,2β-Epoxy-4-methylene-5β-cholestan-3-one (**4**). The same reaction with 1β,2β-epoxy-5β-cholestan-3-one[3] (250 mg) after 5 h reflux was processed as above. Chromatography on silica (elution with hexane-ether 9·6:0·4) gave a colorless oil (125 mg, 48%) recrystallized from MeOH, m.p. 98–99°; $[\alpha]_D$ + 53° (*c*, 1·01); λ_{max} 240 nm (ϵ 4500); ν_{max} 1692 and 1607 cm^{-1}. NMR: δ 6·37 and 5·46 (4-CH_2, two m), 3·46 (1-H and 2-H, narrow m), 1·34 (19-H, s) and 0·66 (18-H, s). (Found: C, 81·42; H, 10·88; M^+ 412; $C_{28}H_{44}O_2$ requires: C, 81·50; H, 10·75%, M.W. 412·6).

5α-Cholestan-4-methylene-1α,3β-diol (**5a**). A soln of **2** (1·0 g) in dry Et_2O (40 ml) was added dropwise to a slurry of LAH (1·0 g) in dry Et_2O (30 ml) and refluxed for 3 h. Following work up with EtOAc and aq Na_2SO_4 and solvent evaporation, the crude product was recrystallised from MeOH (600 mg, 60%) m.p 143–145°; $[\alpha]_D$ + 65° (*c*, 1·0); NMR: δ 5·07 and 4·67 (4-CH_2, two narrow m), 4·39 (3-H, broad m), 3·81 (1-H, tr), 0·68 (19-H, s) and 0·66 (18-H, s). (Found: M^+ 416; $C_{28}H_{48}O_2$ requires: M.W. 416·6). The *diacetate* (**5b**) was obtained by acetylation with Ac_2O and pyridine overnight at room temp, m.p. 130–131° (MeOH), $[\alpha]_D$ + 67° (*c*, 1·01), ν_{max} 1727 cm^{-1}; NMR: δ 5·42 (3-H, broad m), 4·96 (1-H, t), 5·07 and 4·73 (4-CH_2, two narrow m), 2·12 (1α-OAc and 3β-OAc, s), 0·78 (19-H, s) and 0·66 (18-H, s). (Found: C, 76·80; H, 10·56; M^+ 500; $C_{32}H_{52}O_4$ requires: C, 76·75; H, 10·47%, M.W. 500·7).

1α,2α-Epoxy-4-methylene-5α-cholestan-3β-ol (**6a**). To a soln of **2** (250 mg) in MeOH (40 ml), $NaBH_4$ (250 mg) was added over a few min. The soln was stirred for 2 h at room temp, neutralised with dil HCl, most of the solvent removed, the product precipitated with water, dried (240 mg, 95%) and crystallised twice from MeOH, as long needles, m.p. 137–139°; $[\alpha]_D$ + 79·5° (*c*, 1·12); NMR: δ 5·18 and 4·70 (4-CH_2, two narrow m), 4·38 (3-H, narrow m), 3·13 (1-H and 2-H, narrow m), 0·81 (19-H, s) and 0·67 (18-H, s). (Found: C, 81·33; H, 11·18; M^+ 414; $C_{28}H_{46}O_2$ requires: C, 81·10; H, 11·18%; M.W. 414·6). The *acetate* (**6b**) was obtained as usual, m.p. 96–98° (CH_2Cl_2-MeOH); $[\alpha]_D$ + 74° (*c*, 0·5); ν_{max} 1742 cm^{-1}; NMR: δ 5·50 (3-H, narrow m), 4·87 and 4·67 (4-CH_2, two narrow m), 3·08 (1-H and 2-H, narrow m), 2·17 (3β-OAc, s), 0·82 (19-H, s) and 0·66 (18-H, s). (Found: M^+ 456; $C_{30}H_{48}O_3$ requires: M.W. 456·6). LAH reduction of **6a** afforded diol **5a**.

1α,2α-Epoxy-3β-acetoxy-5α-cholestan-4-one (**7**). Ozonolysis of **6b** (1·0 g) in EtOAc (50 ml) at 0° (15 min) was followed by reductive work up with AcOH (10 ml) and Zn (1·0 g). After filtration H_2O was added, the product Et_2O extracted and the ethereal soln washed with H_2O and aq $NaHCO_3$. Evaporation of solvent gave residue which was recrystallised 3× from MeOH (270 mg, 27%), m.p. 150–152°; $[\alpha]_D$ − 21° (*c*, 1·02); ν_{max} 1751 and 1730 cm^{-1}; NMR: δ 5·33 (3-H, s), 3·29 (1-H and 2-H, s), 2·19 (3β-OAc, s), 0·90 (19-H, s) and 0·67 (18-H, s). (Found: C, 75·63; H, 9·94; M^+ 458; $C_{29}H_{46}O_4$ requires: C, 75·94; H, 10·11%; M.W. 458·6).

Attempts to remove the 3-keto group in **2**. (a) *The mixed hydride method.*[7,8] **2** (1·0 g) in dry Et_2O (40 ml) was added dropwise to a stirred slurry of LAH (1·0 g) in dry Et_2O (30 ml), refluxed for 3 h and cooled; $AlCl_3$ (1·0 g) in dry Et_2O (60 ml) was added dropwise, refluxed for 30 min, cooled and submitted to the same work up as **5a**. The crude product (760 mg) recrystallised from MeOH and was found identical with **5a**.

(b) *The tosyl-hydrazine-$NaBH_4$ method.*[10] A methanolic (125 ml) soln of **2** (500 mg) containing tosyl-hydrazine (250 mg) was left overnight at room temp, then $NaBH_4$ (1·0 g) was added and the mixture refluxed for 6 h. The resulting soln was neutralised with dil HCl, concentrated to small volume, H_2O added and the product Et_2O extracted; the ethereal layer was washed with aq $NaHCO_3$ and H_2O, dried and evaporated in vacuum to a colorless foam, which was chromatographed on alumina; elution with hexane-ether 9·8:0·2 gave *1-hydroxy-4-methylene-1,2-seco-5α-cholest-2-yne* (**8a**) (105 mg, 22%) crystallised from MeOH (with a few drops of CH_2Cl_2)-H_2O, m.p. 106–107°; $[\alpha]_D$ + 35° (*c*, 0·59); λ_{max} 223 nm (ϵ 9700) and 231 nm (shoulder); ν_{max} 3300 cm^{-1}; NMR: δ 5·61

and 5·37 (4-CH_2, two narrow m), 3·44 (1-methylene protons, s), 2·96 (2-H, s, acetylenic proton), 0·72 (19-H, s) and 0·66 (18-H, s). (Found: C, 84·31; H, 11·58; M^+ 398; $C_{28}H_{46}O$ requires; C, 84·35; H, 11·63%; M.W. 398·6). The *acetate* (**8b**) was obtained by the usual method as a colorless oil, homogeneous on TLC, which could not be induced to crystallise; ν_{max} 3333 and 1724 cm^{-1}; NMR: δ 5·59 and 5·27 (4-CH_2, two narrow m), 4·04 and 3·77 (1-methylene protons, AB dd, *J* 12 Hz), 2·91 (2-H, s, acetylenic proton), 2·07 (1-OAc, s), 0·88 (19-H, s) and 0·66 (18-H, s). Further elution with hexane-ether 5:5 gave *5α-cholestane-4-methylene-2β-methoxy-1α,3β-diol* (**9a**) (100 mg, 18%), m.p. 160–162° (MeOH); $[\alpha]_D$ + 74·5° (*c*, 0·79); NMR: δ 5·14 and 4·76 (4-CH_2, two narrow m), 4·31 (3-H, m), 3·96 (1-H, d, *J* 3·5 Hz), 3·63 (2-H, m), 3·41 (2β-OMe, s), 0·79 (19-H, s) and 0·66 (18-H, s). (Found: C, 78·22; H, 11·13; M^+ 446; $C_{29}H_{50}O_3$ requires: C, 77·97; H, 11·28%, M.W. 446·6). The *diacetate* (**9b**) was obtained by acetylation of **9a** for 48 h at room temp; chromatography on silica (elution with hexane-ether 8:2) afforded pure **9b**, m.p. 105–107° (MeOH); $[\alpha]_D$ + 64° (*c*, 0·43); ν_{max} 1742 cm^{-1}; NMR: δ 5·40 (3-H, m), 5·09 (1-H, d, *J* 3·5 Hz), 5·00 and 4·80 (4-CH_2, two m), 3·61 (2-H, m), 3·47 (2β-OMe, s), 2·17 and 2·11 (1α-OAc and 3β-OAc, two s), 0·92 (19-H, s) and 0·64 (18-H, s). (Found: C, 74·76; H, 10·40; M^+ 530; $C_{33}H_{54}O_5$ requires: C, 74·67; H, 10·26%, M.W. 530·7).

Compound **6a** remained unchanged on treatment with tosyl-hydrazine in MeOH overnight at room temp or even after 6 h reflux. After addition of $NaBH_4$ and reflux for 5 h, starting **6a** was partially converted into **9a**. When **6a** was stored overnight in MeOH in the presence of toluene-*p*-sulphonic acid, a mixt of **9a** and unreacted **6a** was obtained. The same reaction performed at reflux for 2 h resulted in quantitative conversion into **9a**.

Tosyl-hydrazine-$NaBH_4$ treatment of other epoxy-ketones. (a) The reaction was done with **1**[5] (250 mg) as described for **2**. Chromatography on alumina (elution with hexane-ether 9:1) gave **11** (*1α,2α-epoxy-3,3-dimethoxy-5α-cholestane*) (40 mg, 15%), m.p. 147–148° (CH_2Cl_2-MeOH); $[\alpha]_D$ + 1° (*c*, 0·54), NMR: δ 3·40 and 3·25 (3α- and 3β-OMe, two s), 3·13 (1-H and 2-H, narrow m), 0·86 (19-H, s) and 0·66 (18-H, s). (Found: C, 77·92; H, 11·09; M^+ 446; $C_{29}H_{50}O_3$ requires: C, 77·97; H, 11·28%; M.W. 446·6); (by treatment with toluene-*p*-sulphonic acid in acetone, overnight at room temp, **11** was reconverted to **1**). Further elution with hexane-ether 6:4 afforded the fragmentation product *1-hydroxy-1,2-seco-5α-cholest-2-yne* (**10a**) (80 mg, 32%) m.p. 97–98° (MeOH); $[\alpha]_D$ + 6° (*c*, 0·77); ν_{max} 3252 cm^{-1}; NMR: δ 3·48 (1-methylene protons, s), 1·96 (2-H, narrow signal, acetylenic proton), 0·63 (19-H, s) and 0·59 (18-H, s). (Found: C, 83·75; H, 11·75; M^+ 386; $C_{27}H_{46}O$ requires: C, 83·87; H, 11·99%; M.W. 386·6). The *acetate* **10b** was prepared as usual and crystallised from MeOH, m.p. 85–87°; $[\alpha]_D$ + 1° (*c*, 0·33); ν_{max} 3288 and 1727 cm^{-1}; NMR: δ 3·95 (1-methylene protons, s), 2·07 (1-OAc, s), 1·94 (2-H, narrow signal, acetylenic proton), 0·69 (19-H, s) and 0·64 (18-H, s). (Found: C, 81·03; H, 11·21; M^+ 428; $C_{29}H_{48}O_2$ requires: C, 81·25; H, 11·29%; M.W. 428·6). Final elution of the column with $CHCl_3$ gave *2β-methoxy-5α-cholestane-1α,3β-diol* (**12a**) (30 mg, 11%), long needles, m.p. 198–200° ($CHCl_3$-MeOH); $[\alpha]_D$ + 43° (*c*, 0·63); NMR: δ 3·95 (3-H, m, overlapping the signal of the 1-H), 3·45 (2β-OMe, s, overlapping the signal of the 2-H), 0·92 (19-H, s) and 0·67 (18-H, s). (Found: C, 77·50; H, 11·35; M^+ 434; $C_{28}H_{50}O_3$ requires: C, 77·36; H, 11·59%; M.W. 434·6). The *diacetate* (**12b**) was obtained by acetylation of **12a** for 48 h at room temp; chromatography on silica (elution with hexane-ether 8·5:1·5) gave pure **12b**, m.p. 94–96° (CH_2Cl_2-MeOH); $[\alpha]_D$ + 26·5° (*c*, 1·0); ν_{max} 1724 cm^{-1}; NMR: δ 5·04 (1-H, d, *J* 3·5 Hz), 4·85 (3-H, m), 3·48 (2β-OMe, s, overlapping the signal of the 2-H), 2·06 (1α-OAc and 3β-OAc, s), 1·02 (19-H, s) and 0·63 (18-H, s). (Found: C, 74·28; H, 10·31; M^+ 518; $C_{32}H_{54}O_5$ requires: C, 74·09; H, 10·49%; M.W. 518·7).

(b) The reaction was performed with *1β,2β-epoxy-5α-cholestan-3-one*[6] (100 mg) as described for **2**. Chromatography on alumina (elution with hexane-ether 6:4) gave **10a** in 25% yield, identical in all respects with the sample obtained from **1**.

(c) The same reaction was attempted on **4**, *1β,2β-epoxy-5β-cholestan-3-one*,[3] *1α,2α-epoxy-cholest-4-en-3-one*,[18] *1α,2α-epoxy-cholesta-4,6-dien-3-one*[3] and *4β,5β-epoxy-cholest-1-en-3-one*,[19] as described for **2**. Repeated chromatography gave no pure products.

$NaBH_4$ treatment of **1**. (a) *At room temperature.* To a soln of **1**[5] (400 mg) in MeOH (60 ml), $NaBH_4$ (500 mg) was added over a few min; after 2 h at room temp the mixture was processed as for **6a**. Chromatography on silica (elution with hexane-ether 7·5:2·5) gave *1α,2α-epoxy-5α-cholestan-3α-ol* (**13a**) (140 mg) recrystallised from MeOH, m.p. 134–135°; $[\alpha]_D$ + 7·5° (*c*, 1·0), NMR: δ 4·07 (3-H, narrow m, $W_{\frac{1}{2}}$ ~ 8 Hz), 3·38 (2-H, t, *J* 4 Hz), 3·23 (1-H, d, *J* 4 Hz), 0·85 (19-H, s) and 0·67 (18-H, s). (Found: C, 80·69; H, 11·36; M^+ 402; $C_{27}H_{46}O_2$ requires: C, 80·54; H, 11·52%; M.W. 402·6). Further elution with the same solvent gave a mixture of **13a** and **14a**, followed by pure *1α,2α-epoxy-5α-cholestan-3β-ol* (**14a**) (205 mg), recrystallised from MeOH, m.p. 119–120°; $[\alpha]_D$ + 26·5° (*c*, 1·0); NMR: δ 4·03 (3-H, broad m, $W_{\frac{1}{2}}$ ~ 18 Hz), 3·07 (1-H and 2-H, narrow m), 0·93 (19-H, s) and 0·67 (18-H, s). (Found: C, 80·40; H, 11·33; M^+ 402; $C_{27}H_{46}O_2$ requires: C, 80·54; H, 11·52%; M.W. 402·6). Acetylation of **13a** by the usual method followed by chromatography on silica (elution with hexane-ether 9:1) gave **13b**, m.p. 111–113° (CH_2Cl_2-MeOH), $[\alpha]_D$ − 27·5° (*c*, 0·87); ν_{max} 1718 cm^{-1}; NMR: δ 5·15 (3-H, t), 3·37 (2-H, t, *J* 4 Hz), 3·15 (1-H, d, *J* 4 Hz), 2·11 (3α-OAc, s), 0·84 (19-H, s) and 0·67 (18-H, s). (Found: M^+ 444; $C_{29}H_{48}O_3$ requires: M.W. 444·6). Acetylation of **14a** gave **14b**, recrystallised from EtOH, m.p. 118–119° (lit.[6]: m.p. 111–113°); NMR: δ 4·98 (3-H broad m), 3·06 (1-H and 2-H, narrow band), 2·07 (3β-OAc, s), 0·94 (19-H, s) and 0·67 (18-H, s).

(b) *At reflux.* To a soln of **1**[5] (100 mg) in MeOH (15 ml), $NaBH_4$ (200 mg) was added over a few min; the mixture was stirred for 2 h at room temp, then refluxed for 4 h. after usual work up and isolation with $CHCl_3$, the crude product was chromatographed on silica; elution with hexane-ether 7:3 gave **13a** (42 mg, 42%). Further elution with hexane-ether 2:8 gave **12a** (60 mg, 54%).

$NaBH_4$ treatment of **14a**. A methanolic (10 ml) soln of **14a** (50 mg) was heated to reflux for 4 h with $NaBH_4$ (100 mg). Following the usual work up **12a** (48 mg), homogeneous on TLC, was isolated.

Compound **13a** remained unchanged when heated to reflux with $NaBH_4$ in MeOH even for 48 h.

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