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Photochemically Induced Mercuric Oxide - Iodine Oxidation of Some Unsaturated Steroid Compounds

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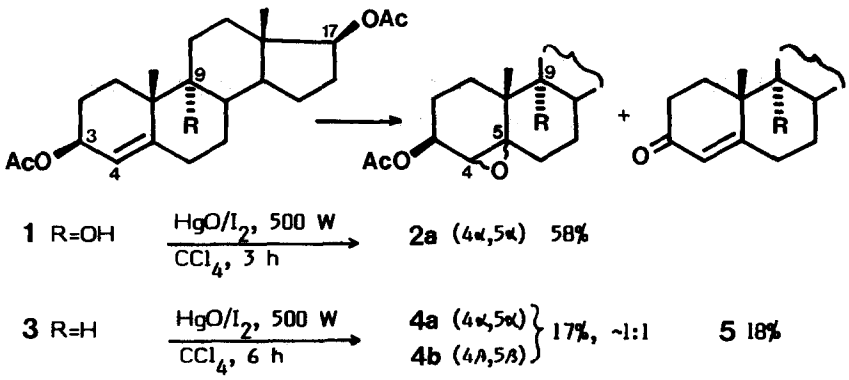
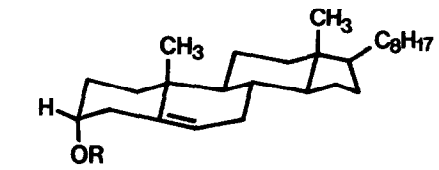
Abstract: *Photochemically induced HgO/I_2 oxidation of cholest-5-en-3α-ol (**6**) and cholest-5-en-3β-ol (**7**) afforded (Scheme 3) products arising from the corresponding alkoxy radicals (**12**, **13** and **14a,b**) and from attack of the I_2O intermediate at the olefinic double bond (epoxides **15a** and **16a,b**, respectively). With cholest-5-ene-1α,3β-diol 3-acetate (**8**) and cholest-7-ene-3β,5α-diol 3-acetate (**9**) the HgO/I_2 oxidation led to unresolvable complex mixtures (Sheme 5). With the same reagent cholest-5-en-3α-ol acetate (**10**) and cholest-5-en-3β-ol acetate (**11**) underwent exclusively attack by I_2O, to give epoxides **20a,b**, iodohydrin **21**, and rearranged products **19** and **22** (Scheme 7), in the case of **10**, and predominantly epoxides **23a,b** (Scheme 8), in the case of **11**.*

In a previous communication[1] we reported that photochemically induced mercury oxide - iodine oxidation of androst-4-ene-3β,9α,17β-triol 3,17-diacetate (**1**) (Scheme 1), carried out with a large excess of oxidant in carbon tetrachloride solution for 3 h at room temperature, resulted in stereospecific α-epoxidation of the olefinic Δ^4-double bond to give as the only defined product 4α,5-epoxy-5α-androstane-3β,9α,17β-triol 3,17-diacetate (**2**) (in 58% yield), while the rest was a complex mixture. On the other hand, when similar HgO/I_2 oxidation was performed with the corresponding 9α-desoxy analogue, i.e., androst-4-ene-3β,17β-diol diacetate (**3**) (Scheme 1), the reaction took place with decreased efficiency (after 6 h irradiation 32% of the starting material remained unchanged) and resulted in a non-stereospecific attack of oxygen at the Δ^4-double bond to produce a ~1:1 mixture of 4α,5α- and 4β,5β-epoxides **4a** and **4b**, in not over 17% yield; the other isolated products being testosterone acetate (**5**) (18%) and a complex mixture (Scheme 1). The observed difference in reactivity between the 9α-hydroxy derivative **1** and the 9α-desoxy compound **3** strongly indicated that the 9α-hydroxy group in **1** plays an important role in oxygen addition, affecting both the stereochemistry and the efficiency of epoxidation at the olefinic Δ^4-double bond.



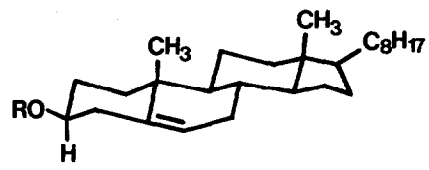
Scheme 1.

These results and the fact that epoxidation of the olefinic double bond with the HgO/I_2 reagent had not been previously observed[2], prompted us to investigate the action of this reagent on some other unsaturated steroid compounds, including homoallylic alcohols in which the hydroxy group (secondary or tertiary) and the olefinic double bond are incorporated in the steroid moiety in various mutual orientations, such as: cholest-5--en-3α-ol (**6**)[4], cholest-5-en-3β-ol (**7**), cholest-5-ene-1α,3β-diol 3-acetate (**8**)[5] and cholest-7-ene-3β,5α-diol 3-acetate (**9**)[6], as well as the corresponding homoallylic acetates, cholest-5-en-3α-ol acetate (**10**) and cholest--5-en-3β-ol acetate (**11**).



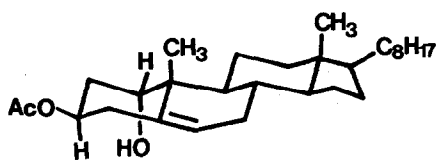
6 R=H

10 R=Ac



7 R=H

11 R=Ac



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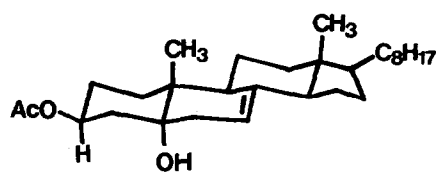

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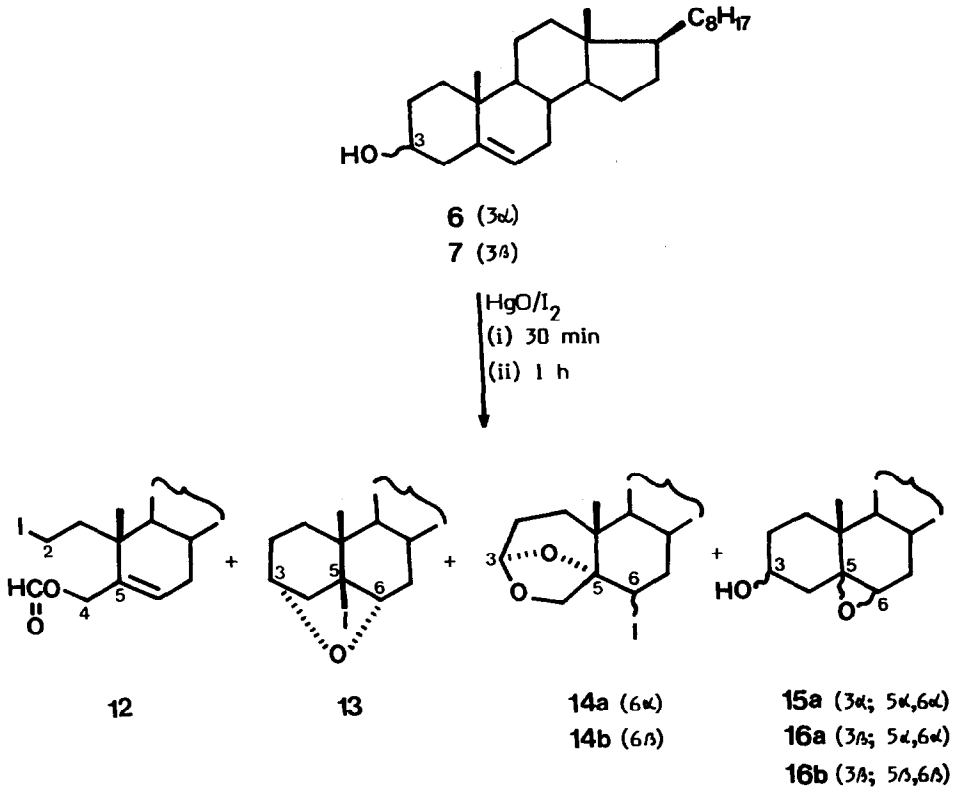
Scheme 2.

Results and Discussion

The oxidations of the homoallylic alcohols **6** - **9** were carried out with a large excess of HgO/I_2 reagent (the mol-ratio substrate/HgO/I_2 being : (i) 1:8:8, and (ii) 1:5:5) in carbon tetrachloride solution by irradiation with a 500 W tungsten lamp at room temperature, until practically all starting material was consumed. The reaction mixtures were separated by column chromatography on silica gel. The following comments can be made about the results obtained.

When subjected to HgO/I_2 oxidation, using the mol-ratio (i) for 30 min, and the mol-ratio (ii) for 1 h, cholest-5-en-3α-ol (**6**) afforded (Scheme 3, Table 1) 3-formyloxy-2-iodo-A-nor-2,3-secocholest-5-ene (**12**) (yield: 16.1% for (i), 21.8% for (ii)), 3α,6α-epoxy-5-iodo-5β-cholestane (**13**) (yield: 16.7% for (i), 4.4% for (ii)), the epimeric 6α- and 6β-iodo-3α,5-epoxy-A-homo-4-oxa-5α-cholestanes (**14a** and **14b**) (yield: 2.3% and 5.2%, respectively, only for (ii)), and 5,6α-epoxy-5α-cholestan-3α-ol (**15a**) (yield: 38.9% for (i), 5.2% for (ii)).



(i) mol-ratio substrate/HgO/I_2 = 1:8:8; (ii) mol-ratio substrate/HgO/I_2 = 1:5:5.

Scheme 3.

Table 1. Products Obtained by HgO/I_2 Oxidation of the Unsaturated Alcohols **6** and **7**

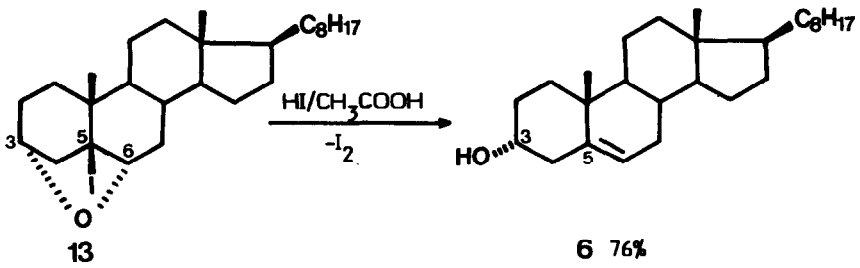
		Yields/% of reaction products[a]						
Substrate	Procedure[b,c]	**12**	**13**	**14a**	**14b**	**15a**	**16a**	**16b**
6	(i)	16.1	16.7			38.9		
6	(ii)	21.8	4.4	2.3	5.2	5.2		
7	(i)	29.2		14.6[d]			24.0[e]	
7	(ii)	34.2		13.9[d]			2.8[e]	

a) All yields refer to crude products isolated by column chromatography on silica-gel. b) (i) Mol-ratio substrate /HgO/I_2 = 1:8:8. c) (ii) Mol-ratio substrate /HgO/I_2 = 1:5:5. d) Ratio **14a/14b** ~ 7:3. e) Ratio **16a/16b** ~ 1:1.

On the other hand, similar oxidation of cholest-5-en-3β-ol (**7**) gave (Scheme 3, Table 1) the formyloxy iodo derivative **12** (yield: 29.2% for (i), 34.2% for (ii)), the epimeric 6α- and 6β-iodo-3α,5α-epoxides **14a** and **14b** (total yield: 14.6% for (i), 13.9% for (ii); ratio ~7:3), and a ~1:1 mixture of 5,6α-epoxy-5α-cholestan-3β--ol (**16a**) and 5,6β-epoxy-5β-cholestan-3β-ol (**16b**) (total yield being 24.0% for (i), 2.8% for (ii)).

The reaction products **12** - **16** were fully characterized by their analytical and spectral data and/or by comparison with compounds of known structures. IR and ^{1}H-NMR spectral characteristics of the iodoformate **12** and 6α- and 6β-iodo-3α,5α-epoxides **14a** and **14b** were identical to those reported in the literature.[7,8]

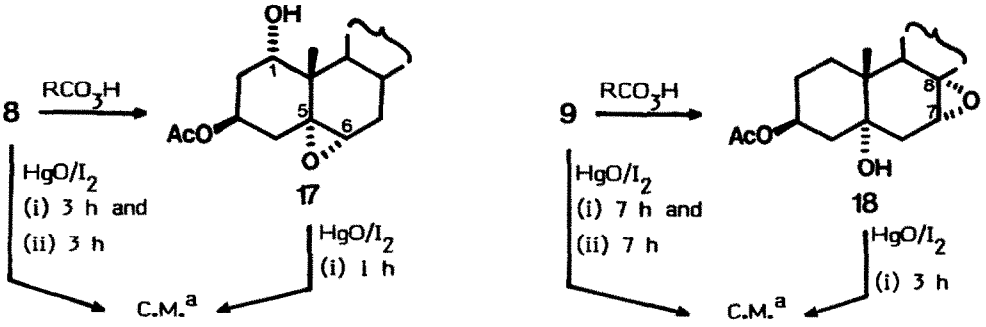
Compound **13** ($C_{24}H_{45}OI$) was identified as 3α,6α-epoxy-5-iodo-5β-cholestane on the basis of its mass spectrum (*m/z* 385 ($M^{+\cdot}$ - 127, 100%)), IR spectrum (absence of OH group) and ^{1}H- and ^{13}C-NMR spectral data. The ^{1}H-NMR spectrum of **13** shows an ABX signal at δ 2.50 and 2.56 ppm arising from $H_2C(4)$, a broad doublet at δ 4.07 ppm and a double doublet at δ 4.62 ppm, attributable to Hβ-C(3) and Hβ-C(6), respectively, while the downfield shift of the $CH_3(19)$ group (at δ 1.23 ppm) suggested the 5β-configuration of the iodine atom. Moreover, the number of primary, secondary, tertiary, and H-free C-atoms detectable in the ^{1}H-decoupled ^{13}C-NMR spectrum of this compound (8 CH (two being attached to O), 11 CH_2, 5 CH_3, and 3 quaternary C (none attached to O)) is in complete agreement with structure **13**. Besides, chemical evidence of the proposed structure was obtained by opening of the tetrahydrofuran ring with HI in acetic acid, which resulted, upon iodine elimination, in the formation of cholest-5-en-3α-ol (**6**) (Scheme 4).



Scheme 4.

Epoxides **15a**, **16a** and **16b** were directly compared with the corresponding epoxy compounds prepared by known procedures.[9,10]

Mercuric oxide - iodine oxidations of the homoallylic alcohols **8** and **9** (performed under experimental conditions (i) or (ii), for 3 h in the case of **8**, and 7 h in the case of **9**[11]) gave only complex unresolvable mixtures, in which the corresponding epoxides **17** and **18** could not be detected (TLC). The epoxy derivatives **17** and **18** (prepared by *m*-chloroperbenzoic acid oxidation of compounds **8** and **9**, respectively), were separately treated with an excess of the HgO/I_2 reagent (8 mol-equivalents for 1 h and 3 h, respectively, i.e., until consumption of the substrates), producing again unresolvable mixtures as the sole reaction products (Scheme 5). The latter experiments showed that epoxides **17** and **18** reacted with mercuric oxide and iodine faster than the corresponding unsaturated hydroxy derivatives **8** and **9**; therefore, due to their higher reactivity, they could not be found among the oxidation products of **8** and **9**, even if primarily formed.



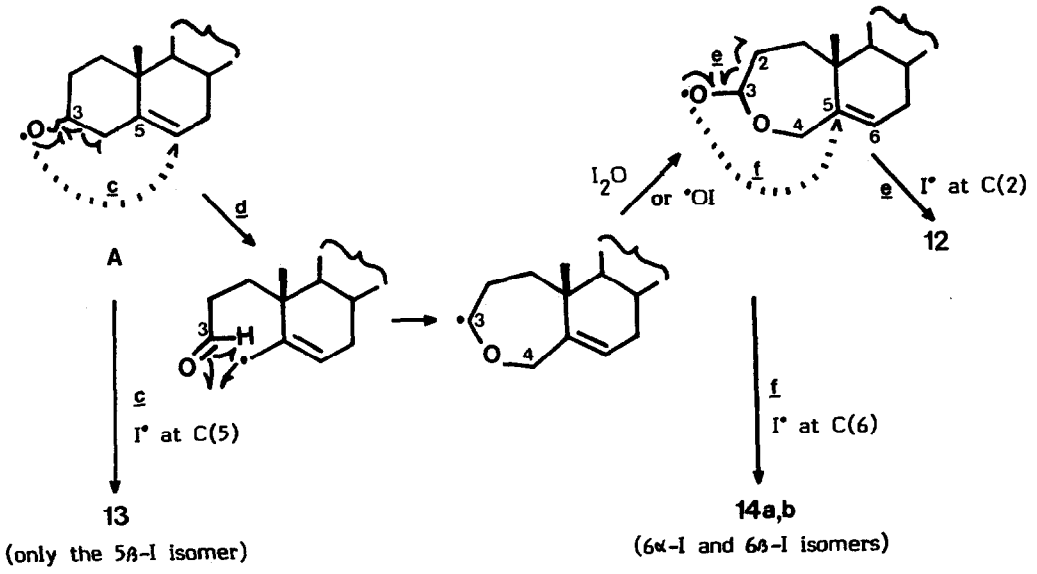
(i) mol-ratio substrate/HgO/I_2 = 1:8:8; (ii) mol-ratio substrate/HgO/I_2 = 1:5:5.
[a] C.M. = complex mixture.

Scheme 5.

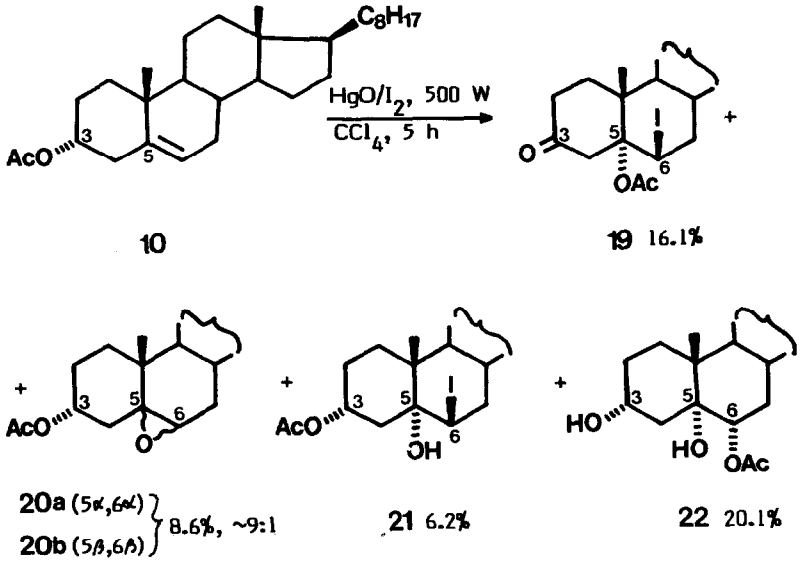
The results obtained with cholest-5-en-3α-ol (**6**) and cholest-5-en-3β-ol (**7**) indicate that most of the reactivity of these secondary homoallylic alcohols can be explained by participation of the alkoxy radical **A**, which undergoes stabilization in various ways (c, d, e and f)[12] to give compounds **12** - **14** (Scheme 6).

In order to suppress the above free-radical processes which compete with epoxidation at the olefinic double bond in the homoallylic alcohols **6** and **7**, their hydroxy group was protected by acetylation. The resulting cholest-5-en-3α-ol acetate (**10**) and cholest-5-en-3β-ol acetate (**11**) were then subjected to similar photochemically induced HgO/I_2 oxidation (using procedure (i), which in the case of alcohols **6** and **7** favoured epoxide formation).

Cholest-5-en-3α-ol acetate (**10**) (after 5 h oxidation) afforded (Scheme 7) 6β-iodo-5α-hydroxy-cholestan-3-one acetate (**19**) (16.1%), 5,6α-epoxy-5α-cholestan-3α-ol acetate (**20a**) and 5,6β-epoxy--5β-cholestan-3α-ol acetate (**20b**) (total yield 8.6%, ratio ~9:1), 6β-iodo-5α-cholestane-3α,5-diol 3-acetate (**21**) (6.2%) and 5α-cholestane-3α,5,6α-triol 6-acetate (**22**) (20.1%) (the rest was unchanged starting material **10** (recovered in 2.5% yield) and a complex mixture).



Scheme 6.

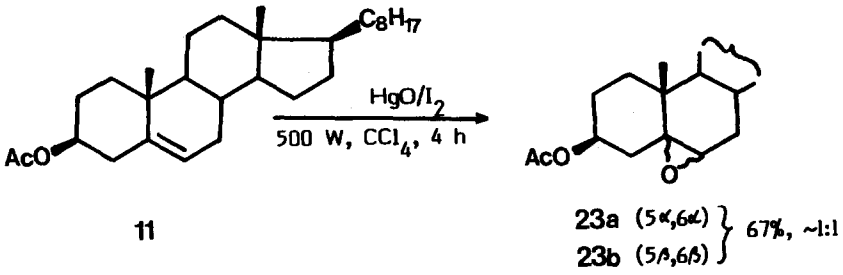


Scheme 7.

The reaction products **19** - **22** were fully characterized by their analytical and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra) (see Experimental); besides, structures **19** and **21** were confirmed by chemical methods.

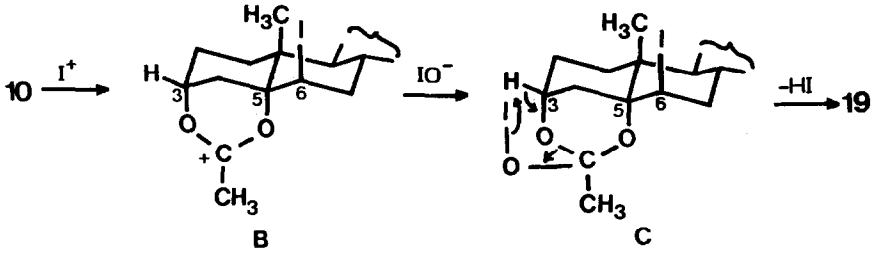
The acetoxy iodoketone **19** ($C_{29}H_{47}IO_3$) was reduced with lithium aluminium hydride to give a mixture of epimeric 3α,5α- and 3β,5α-cholestanediols (in 20.5 and 6.4% yield) and, in addition, cholest-5-en-3α-ol and cholest-5-en-3β-ol (in 5.4% and 38.9% yield), indicating that this compound contained a 3-keto and a 5α-OAc group. The 6β-configuration of iodine was deduced from the strong downfield shift of the CH_3(19) signal in the ^{1}H-NMR spectrum of **19** (δ = 1.67 ppm) (due to 1,3-diaxial deshielding interaction by the iodine). On the other hand, the iodohydrin **21** ($C_{29}H_{49}IO_3$) was transformed, with a 5% methanolic KOH solution, to 5,6α--epoxy-5α-cholestan-3α-ol, thus confirming the proposed structure for this derivative.

In contrast to its 3α-epimer **10**, when cholest-5-en-3β-ol acetate (**11**) was treated with HgO/I_2 (for 4 h), it underwent mainly non-stereospecific epoxidation of the olefinic double bond (Scheme 8) to produce a ~1:1 mixture of 5α,6α- and 5β,6β-epoxides **23a** and **23b** (in 67% yield)[10] (while the rest was an undistinguishable mixture which was not further investigated).



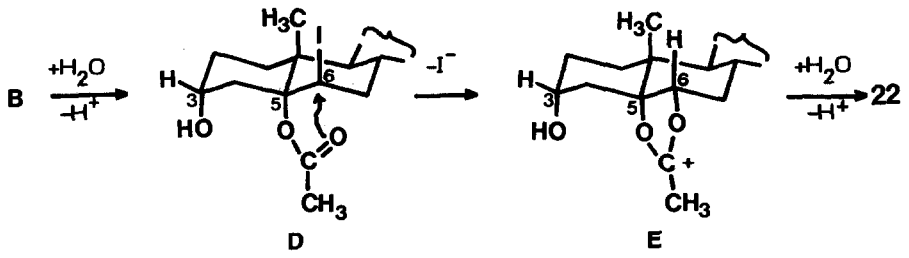
Scheme 8.

The results obtained in the HgO/I_2 oxidation of cholest-5-en-3α-ol acetate (**10**) show that the reactive intermediate in this oxidative process is iodine oxide (I_2O), which is generated *in situ* from HgO and I_2. The fragments of this species (I^+ and IO^-) undergo electrophilic addition to the Δ^5-double bond of **10** to give the iodohydrin **21** (Scheme 7). Besides, the reaction can also proceed by participation of the 3α-acetoxy group, involving (1) either a single migration of this group to the C(5) center (Scheme 9) with the formation of the



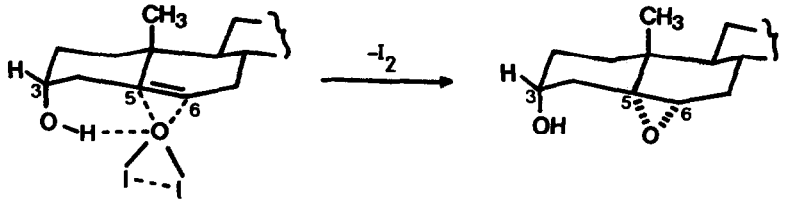
Scheme 9.

intermediate **B**, followed by attack of the IO^- fragment at the carbocationic site of **B** to produce the intermediate **C**, which, upon elimination of HI, finally affords the ketone derivative **19**; or (2) it may involve a double acetoxy group migration to the C(6) position (Scheme 10), resulting (by way of the intermediates **B**, **D** and **E**) in the formation of the 3α,5α,6α-triol 6-acetate **22**.



Scheme 10.

The same intermediate iodine oxide species (I_2O) is probably also involved in the observed epoxidation of the steroid derivatives **1**, **3**, **6**, **7**, **10** and **11**. It can be assumed that this species "transfers" its oxygen to the olefinic double bond simultaneously with elimination of iodine. An axial homoallylic hydroxy group in the transition state of the reaction increases the electrophilicity of oxygen in the state of formation by way of an intermolecular hydrogen bond, thus affecting both the stereochemistry and the efficiency of epoxidation (Scheme 11). The exclusive formation of the α-epoxides **2** and **15a** from the 9α-hydroxy-androstene derivative **1** and cholest-5-en-3α-ol (**6**), respectively, can be ascribed to such an interaction. In substrates in which hydrogen bonding interaction with I_2O does not exist (due to the absence of the OH group or its unsuitable spatial orientation), the probability of the I_2O approch from the back-side (α) or front-side (β) to the olefinic double (in the absence of other factors) is similar, and therefore approximately equimolar mixtures of the stereoisomeric epoxides are produced. Thus, as described above, mixtures of α- and β-epoxides (~1:1) are formed in the HgO/I_2 oxidation of the 9α-desoxy androst-5-ene compound **3**, cholest-5-en-3β-ol (**7**) and its acetate **11**, while in cholest-5-en-3α-ol acetate (**10**) (contrary to the 3α-alcohol **6**), α-epoxidation is only a minor process.



Scheme 11.

EXPERIMENTAL[14]

General. Removal of solvents was carried out under reduced pressure. Prep. column chromatography: silica gel 0.063-0.2 mm. TLC: control of reactions and separation of products on silica gel G (*Stahl*) with benzene/EtOAc 9:1 or 7:3, detection with 50% H_2SO_4 soln. M.ps: uncorrected. IR spectra: *Perkin-Elmer-337* spectrophotometer; ν in cm^{-1}. NMR spectra: *Varian FT 80A*, *Varian Gemini* or *Brucker AM-360* (^1H at 80, 200 or at 360 MHz, ^{13}C at 90.55 MHz); $CDCl_3$ soln. at r.t., TMS as internal standard; chemical shifts in ppm as δ values, *J* in Hz. Mass spectra: *Finnigan-MAT 8230*. Light petroleum refers to the fraction boiling at 40-60 °C.

General procedures for mercuric oxide - iodine oxidations. - A mixture of substrate **6** - **11** (~1.5 - 5 mmol) and an excess of mercuric oxide and iodine (for procedure (i): 8 molar equivalents; for procedure (ii): 5 molar equivalents) in carbon tetrachloride (250 - 500 ml) was stirred and irradiated without heating with a 500 W tungsten lamp placed in a central water- and air-cooled jacket until practically all starting material was consumed. It was then filtered, washed successively with water, 10% aq. $Na_2S_2O_3$, saturated aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to a dryness. The residue was chromatographed on a silica gel column.

Oxidation of cholest-5-en-3α-ol (6) with HgO/I_2. Procedure (i). - A suspension of **6** (2.00 g, 5.17 mmol), HgO (8.96 g, 41.36 mmol) and I_2 (10.54 g, 41.36 mmol) in CCl_4 (500 ml) was irradiated for 30 min to give a mixture (2.12 g), which upon work up as described above, was chromatographed on silica gel (80 g). Elution with light petroleum/benzene 8:2 afforded 3-formyloxy-2-iodo-A-nor-2,3-secocholest-5-ene (**12**) (440 mg, 16.1%) as an oil. (Lit.[7] oil). IR (film): 1726*s*, 1468*m*, 1380*m*, 1160*s*, 845*w*. ^1H-NMR (360 MHz): 0.67 (*s*, 3H, CH_3(18)); 0.87 (*d*, 6H, CH_3(26), CH_3(27)); 0.92 (*d*, 3H, CH_3(21)); 0.99 (*s*, 3H, CH_3(19)), 2.94, 3.08 (two *m*, 2H, H_2C(2)); 4.54, 4.66 (two *d*, 2H, *J* = 12 Hz, H_2C(4)); 5.91 (*d*, 1H, *J* = 6 Hz, H-C(6)); 8.14 (*s*, 1H, OCOH). ^{13}C-NMR: 161.1 (*d*, C(3)); 136.7 (*s*, C(5)); 132.2 (*d*, C(6)); 65.0 (*t*, C(4)); 56.8 (*d*, C(17)); 56.2 (*d*, C(14)); 43.0 (*s*, C(13)); 42.6 (*d*, C(9)); 42.3 (*s*, C(10)); 41.7 (*t*, C(1)); 39.6 (*t*, C(24)); 39.6 (*t*, C(12)); 36.2 (*t*, C(22));5.8 (*d*, C(20)), 31.8 (*t*, C(7)); 31.4 (*d*, C(8)), 28.3 (*t*, C(16)); 28.1 (*d*, C(25)); 24.3 (*t*, C(15)); 23.9 (*t*, C(23)), 23.0 (*q*, C(19)); 22.9 (*q*, C(26)); 22.6 (*q*, C(27)); 20.8 (*t*, C(11)); 18.8 (*q*, C(21)); 11.7 (*q*, C(18)); 1.2 (*t*, C(2)). MS: *m/z* 528 ($M^{+\cdot}$, 24%), 327 (528 - 201, 100%). The next light petroleum/benzene 8:2 fractions eluted 3α,6α-epoxy-5-iodo-5β-cholestane (**13**) (442 mg, 16.7%), m.p. 153 °C (from acetone). $[\alpha]_D^{22}$= -26.3 (c= 1.0, $CHCl_3$). IR (KBr): 1460*m*, 1272*m*, 1060*m*, 992*m*, 922*m*, 878*m*, 840*w*, 772*w*. ^1H-NMR (360 MHz): 0.71 (*s*, 3H, CH_3(18)); 0.87 (*d*, 6H, CH_3(26), CH_3(27)); 0.90 (*d*, 3H, CH_3(21)); 1.23 (*s*, 3H, CH_3(19)); 2.50, 2.56 (*q* and *d*, respectively, ABX, 2H, $J_{gem(AB)}$ = 15 Hz, J_{AX} = 0, J_{BX} = 5 Hz, H_2C(4)); 4.07 (*br.d*, 1H, HC(3)); 4.62 (*dd*, 1H, *J* = 9.5 Hz, 4.5 Hz, H-C(6)). ^{13}C-NMR: 84.8 (*d*, C(6)); 75.9 (*d*, C(3)); 57.7 (*d*, C(17)), 56.0 (*d*, C(14)), 53.3 (*s*, C(10)); 49.7 (*d*, C(9)); 49.2(*t*, C(4)); 43.5 (*s*, C(13)); 41.1 (*s*, C(5)); 40.6 (*t*, C(12)); 39.5 (*t*, C(24); 37.0 (*t*, C(2)); 36.2 (*t*, C(22)), 35.8 (*d*, C(20)); 31.8 (*d*, C(8)); 30.7 (*t*, C(7)), 29.7 (*t*, C(1)); 28.9 (*q*, C(19)); 28.4 (*t*, C(16)); 28.0 (*d*, C(25)); 23.9 (*t*, C(11), C(15), C(23)); 22.8 (*q*, C(26)); 22.6 (*q*,

C(27)), 18.6 (*q*, C(21)); 12.7 (*q*, C(18)). MS: *m/z* 385 ($M^{+\cdot}$ -127, 100%). Anal. calc. for $C_{27}H_{45}IO$ (512.561): C 63.27, H 8.85; C found 63.49, H 8.86. Elution with benzene afforded a complex mixture (150 mg) which was not further investigated. Benzene/Et_2O 9:1 eluted 5,6α-epoxy-5α-cholestan-3α-ol (**15a**) (810 mg, 38.9%), m.p. 126-127 °C (from acetone-methanol; lit.[9] m.p. 125-128°C). IR (KBr): 3525*s*, 1045*m*, 1015*m*. ^{1}H-NMR (80 MHz): 0.60 (*s*, 3H, CH_3(18)); 0.83 (*d*, 6H, CH_3(26), CH_3(27)); 0.87 (*d*, 3H, CH_3(21)); 2.87 (*d*, 1H, J = 4.8 Hz, H-C(6)); 4.07 (*m*, 1H, H-C(3)). MS: *m/z* 402 ($M^{+\cdot}$, 100%), 384 (402 - 18, 49%).

Procedure (ii). - A mixture of **6** (2.00 g, 5.17 mmol), HgO (5.60 g, 25.85 mmol) and I_2 (6.56 g, 25.85 mmol) in CCl_4 was irradiated for 1 h, and the residue (2.08 g), obtained as described above, chromatographed on silica gel (80 g). Light petroleum/benzene 8:2 eluted first 3-formyloxy-2-iodo-A-nor-2,3-secocholest-5-ene (**12**) (596 mg, 21.8%), and subsequently a mixture of 3α,6α-epoxy-5-iodo-5β-cholestane (**13**), 3α,5-epoxy-6α - and 3α,5-epoxy-6β-iodo-A-homo-4-oxa-5α-cholestane (**14a** and **14b**) (381 mg). Benzene/Et_2O 95:5 eluted 300 mg of a complex mixture. Elution with benzene/Et_2O 90:10 gave the 5α,6α-epoxide **15a** (108 mg, 5.2%). More polar benzene/Et_2O and Et_2O fractions contained 419 mg of an undistinguishable mixture which was not further investigated.

Separation of **13**, **14a** *and* **14b**. - The above mixture of compounds **13**, **14a** and **14b** (381 mg) was separated by chromatography on silica gel (20 g), using light petroleum as eluent. The first fraction afforded 3α,6α-epoxy-5-iodo-5β-cholestane (**13**) (118 mg, 4.4%), identified by m.p., mixed m.p. determination and spectral characteristics. The next fraction contained 3α,5-epoxy-6β-iodo-A-homo-4-oxa-5α-cholestane (**14b**) (142 mg, 5.2%), m.p. 79-81°C (from acetone; lit.[7] m.p. 80-81°C). ^{1}H-NMR (80 MHz): 0.70 (*s*, 3H, CH_3(18)); 0.84 (*d*, 6H, CH_3(26), CH_3(27)); 0.87 (*d*, 3H, CH_3(21)); 1.32 (*s*, 3H, CH_3(19)); 3.34 and 4.24 (two *d*, 2H, J = 8 Hz, H_2C(4)); 4.22 (*t*, overlapped with one of H_2C(4) resonance, 1H, H-C(6)); 5.61 (*br.s*, 1H, H-C(3)). Further fractions eluted 3α,5-epoxy-6α-iodo-A-homo-4-oxa-5α-cholestane (**14a**) (64 mg 2.3%), m.p. 146-148 °C (from Et_2O/acetone; lit.[7] m.p. 145-147 °C). ^{1}H-NMR (80 MHz): 0.65 (*s*, 3H, CH_3(18)); 0.85 (*d*, 6H, CH_3(26), CH_3(27)), 0.87 (*d*, 3H, CH_3(21)); 0.90 (*s*, 3H, CH_3(19)); 3.74 and 4.20 (two *d*, 2H, J = 7.5 Hz, H_2C(4)); 4.57 (*q*, 1H, J = 12 Hz, 6 Hz, H-C(6)); 5.55 (*br.s*, 1H, H- C(3)).

Oxidation of cholest-5-en-3β-ol **7** *with HgO/I_2. Procedure (i).* - A suspension of **7** (2.00 g, 5.17 mmol), HgO (8.96 g, 41.36 mmol) and I_2 (10.50 g, 41.36 mmol) in CCl_4 (500 mL) was irradiated for 30 min to give a mixture (2.32 g) which was chromatographed on silica gel (80 g). Elution with light petroleum/benzene 8:2 afforded 3-formyloxy-2-iodo-A-nor-2,3-secocholest-5-ene (**12**) (798 mg, 29.2%). The next light petroleum/benzene 8:2 fractions eluted a ~7:3 mixture (400 mg, 14.6%) of **14a** and **14b** (estimated from intensities of the characteristic ^{1}H-NMR signals for the C(3), C(4), C(6) and C(18) protons of these stereoisomers). Elution with benzene gave a mixture (320 mg) which was not further investigated. Benzene/Et_2O 9:1 fractions contained a ~1:1 mixture (500 mg, 24.0%) of 5,6α-epoxy-5α-cholestan-3β-ol (**16a**) and 5,6β-epoxy-5β-cholestan-3β-ol (**16b**) (estimated from intensities of signals for C(6), C(18) and C(19) protons appearing in the ^{1}H-NMR spectrum of this mixture).

Procedure (ii). - A mixture of **7** (2.00 g, 5.17 mmol), HgO (5.60 g, 25.85 mmol) and I_2 (6.56 g, 25.85 mmol) in CCl_4 (500 mL) was irradiated for 1 h, and the residue (2.10 g), obtained as described above, was

chromatographed on silica gel (80 g). Elution with light petroleum/benzene 8:2 afforded first the formyloxy iodo derivative **12** (936 mg, 34.2%), and then a ~7:3 mixture (390 mg, 13.9%) of the epimeric 6-iodo-3α,5α--epoxides **14a** and **14b** (the ratio estimated from the ^{1}H-NMR spectrum). Benzene and the first benzene/Et_2O 9:1 fractions contained a complex mixture. Further elution with benzene/Et_2O 9:1 afforded a ~1:1 mixture (2.8 mg, 2.8%) of 5α,6α- and 5β,6β-epoxides **16a** and **16b** (estimated from the ^{1}H-NMR spectrum).

Opening of the tetrahydrofuran ring in the iodoether **13**. - A stirred solution of the iodoether **13** (200 mg) in glacial AcOH (5 mL) was treated dropwise with a solution of hydroiodic acid (0.07 mL 57% HI aq.) in glacial AcOH (2 mL). The resulting mixture was left overnight in a refrigerator, diluted with water and extracted with diethyl ether. The etheral layer was washed with water, 10% aq. $Na_2S_2O_3$, water, saturated aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness. The crystalline solid (132 mg, 87.5%) was recrystallized from methanol to give epicholesterol **6** (115 mg, 76.2%), m.p. 140-141 °C (lit.[4] m.p. 141.5 °C).

Epoxidation of cholest-5-ene-1α,3β-diol 3-acetate **8**[5]. - Compound **8** (1.00 g) in CH_2Cl_2 (25 mL) was treated with 85% *m*-chloroperbenzoic acid (500 mg in 25 mL CH_2Cl_2) at room temperature for 1 h. The residue obtained after the usual work up (980 mg, 94.6%) was recrystallized from acetone to give 5,6α-epoxy--5α-cholestane-1α,3β-diol 3-acetate (**17**) (865 mg, 83.5%), m.p. 156 °C. $[\alpha]_D^{19}$ = -11.0 (c = 1.09, $CHCl_3$). IR (KBr): 3450*s*, 1730*s*, 1710*s*, 1275*s*, 1042*m*. ^{1}H-NMR (80 MHz): 0.61 (*s*, 3H, CH_3(18); 0.84 (*d*, 6H, CH_3(26), CH_3(27)); 0.86 (*d*, 3H, CH_3(21)); 1.08 (*s*, 3H, CH_3(19)), 2.02 (*s*, 3H, AcO); 2.82 (*d*, 1H, *J* = 5 Hz, H-C(6)), 3.86 (*t*, 1H, *J* = 2.5 Hz, H-C(1)); 5.30 (*hept*, 1H, *J* = 6 Hz, H-C(3)). Anal. calc. for $C_{29}H_{48}O_4$ (460.703): C 75.61, H 10.50; found: C 75.43, H 10.60.

Epoxidation of 5α-cholest-7-ene-3β,5-diol 3-acetate (**9**)[6]. - Compound **9** (500 mg) in CH_2Cl_2 (10 mL) was treated with 85% *m*-chloroperbenzoic acid (250 mg in 15 mL CH_2Cl_2) at room temperature for 30 min. The usual work up afforded 7α,8α-epoxy-5α-cholestane-3β,5-diol 3-acetate (**18**) (500 mg, 96.5%), which was recrystallized from methanol, m.p. 136 °C. $[\alpha]_D^{19}$ = -10.0 (c = 0.40, $CHCl_3$). IR (KBr): 3460*s*, 1720*s*, 1245*s*, 1030*m*. ^{1}H-NMR (80 MHz): 0.74 (*s*, 3H, CH_3(18)); 0.86 (*d*, 6H, CH_3(26), CH_3(27)); 0.88 (*d*, 3H, CH_3(21)); 1.01 (*s*, 3H, CH_3(19)); 2.00 (*s*, 3H, AcO); 3.51 (*br.s*, 1H, H-C(7)); 5.07 (*hept*, 1H, *J* = 6 Hz, H-C(3)). MS: *m/z* 460 ($M^{+\cdot}$, 32%), 442 (460 - 18, 76%), 400 (460 - 60, 12%), 382 (460 -78, 31%). Anal. calc. for $C_{29}H_{48}O_4$ (460.703): C 75.61, H 10.50; found: C 75.41, H 10.36.

Oxidation of cholest-5-en-3α-ol acetate (**10**) *with HgO/I_2. Procedure (i).* - A suspension of **10** (1.00 g, 2.33 mmol), HgO (4.04 g, 18.64 mmol) and I_2 (4.73 g, 18.64 mmol) in CCl_4 (400 mL) was irradiated for 2 h. The reaction mixture obtained (1.10 g), after the usual work up, was chromatographed on silica gel (40 g). Toluene first eluted the starting acetate **10** (25 mg, 2.5%). The following toluene fractions contained 6β-iodo--5α-hydroxycholestan-3-one acetate (**19**) (215 mg, 16.15%), m.p. 87 °C (from methanol). $[\alpha]_D^{22}$ = -44.3 (c = 0.60, $CHCl_3$). IR (KBr): 1733*s*, 1229*s*, 1215*s*, 758*s*. ^{1}H-NMR (200 MHz): 0.77 (*s*, 3H, CH_3(18)); 0.86 (*d*, 6H, CH_3(26), CH_3(27)); 0.91 (*d*, 3H, CH_3(21)); 1.67 (*s*, 3H, CH_3(19)); 1.99 (*s*, 3H, AcO); 3.30 (AB *q*, $\Delta\delta_{AB}$ = 0.12, 2H, *J* = 15.6 Hz, H_2C(4)); 5.57 (*m*, 1H, H-C(6)). ^{13}C-NMR: 209.0 (*s*, C(3)); 169.7 (*s*, $CH_3\underline{C}OO$); 90.0 (*s*, C(5)); 56.2 (*d*, C(17)); 55.0 (*d*, C(14)); 47.5 (*t*, C(4)); 46.1 (*d*, C(9)); 42.7 (*s*, C(13)); 41.7 (*s*, C(10)); 39.8 (*t*, C(12)); 39.5 (*t*, C(24)); 38.5 (*t*, C(2)); 37.4 (*t*, C(1)); 36.1 (*t*, C(22)); 35.7 (*d*, C(20)); 35.1

(*t*, C(7)); 31.3 (*d*, C(8)); 28.1 (*t*, C(16)); 28.0 (*d*, C(25)); 25.2 (*d*, C(6)); 24.1 (*t*, C(15)); 23.8 (*t*, C(23)); 22.8 (*q*, C(27)); 22.6 (*q*, C(26)); 22.1 (*q*, C(19)); 21.4 (*t*, C(11)); 20.9 (*q*, $\underline{C}H_3COO$); 18.7 (*q*, C(21)); 12.2 (*q*, C(18)). MS: *m/z* 384 ($M^{+\cdot}$ -127, -59, 72%). Anal. calc. for $C_{29}H_{47}IO_3$ (570.60): C 61.05, H 8.30; found: C 61.23, H 8.53.

Elution with toluene/Et_2O 95:5 afforded a mixture (95 mg, 9.2%) of 5,6α-epoxy-5α-cholestan-3α-ol acetate (**20a**) and 5,6β-epoxy-5β-cholestan-3α-ol acetate (**20b**). Selected ^{1}H-NMR signals of **20a** and **20b** in the mixture: (a) arising from the 5α,6α-epoxide **20a**: 0.62 (*s*, 3H, CH_3(18)); 1.06 (*s*, 3H, CH_3(19)); 2.08 (*s*, 3H, AcO); 2.75 (*d*, 1H, *J* = 4.3 Hz, H-C(6)); (b) arising from the 5β,6β-epoxide **20b**: 0.65 (*s*, 3H, CH_3(18)); 0.98 (*s*, 3H, CH_3(19)); 2.03 (*s*, 3H, AcO); 2.99 (*d*, 1H, *J* = 2.6 Hz, H-C(6)); the intensity ratios (a)/(b) of the signals being ~9:1. The mixture was recrystallized from acetone-methanol to give pure 5α,6α-isomer **20a**, m.p. 105 °C. $[\alpha]_D^{22}$ = -30.8 (c = 0.5, $CHCl_3$). IR (KBr): 1736*s*, 1238*s*. ^{1}H-NMR (200 MHz): 0.62 (*s*, 3H, CH_3(18)); 0.87 (*d*, 6H, CH_3(26), CH_3(27)); 0.90 (*d*, 3H, CH_3(21)); 1.06 (*s*, 3H, CH_3(19)); 2,08 (*s*, 3H, AcO); 2.75 (*d*, 1H, *J* = 4.3 Hz, H_β-C(6)); 5.09 (*t*, 1H, *J* = 2.7 Hz, H-C(3)). MS: *m/z* 384 ($M^{+\cdot}$ - 60, 73%), 366 (M+. - 60, - 18, 32%).

Toluene/Et_2O 9:1 eluted 6β-iodo-5α-cholestane-3α,5-diol 3-acetate (**21**) (84 mg, 6.3%), m.p. 131-132 °C. $[\alpha]_D^{27}$ = -6.0 (c = 0.67, $CHCl_3$). IR (KBr): 3447*s*, 1709*s*,1247*m*, 1252*m*. ^{1}H-NMR (200 MHz): 0.74 (*s*, 3H, CH_3(18)); 0.87 (*d*, 6H, CH_3(26), CH_3(27)); 0.92 (*d*, 3H, CH_3(21)); 1.40 (*s*, 3H, CH_3(19)); 2.01 (*s*, 3H, AcO); 2.34 (*dd*, 1H, *J* = 15.5 Hz, 3.4 Hz, H_β-C(4)); 2.85 (*dt*, 1H, *J* = 15.5 Hz, 2.5 Hz, H_α-C(4)); 4.16 (*m*, 1H, H_α-C(6)); 5.46 (*m*, 1H, H-C(3)). ^{13}C-NMR: 171.7 (*s*, $CH_3\underline{C}OO$); 85.4 (*s*, C(5)); 66.5 (*d*, C(3)); 56.2 (*d*, C(17)); 55.2 (*d*, C(14)); 45.6 (*d*, C(9)); 42.8 (*s*, C(13)); 41.7 (*s*, C(10)); 40.0 (*t*, C(12)); 39.5 (*t*, C(4)); 38.3 (*t*, C(7)); 36.2 (*t*, C(22)); 35.8 (*d*, C(20)); 34.4 (*t*, C(24)); 31.2 (*d*, C(8)); 29.0 (*t*, C(1)); 28.2 (*t*, C(16)); 28.0 (*d*, C(25)); 28.0 (*t*, C(2)); 27.2 (*d*, C(6)); 24.1 (*t*, C(15)); 23.8 (*t*, C(23)); 22.9 (*q*, $\underline{C}H_3COO$); 22.8 (*q*, C(27)); 22.6 (*q*, C(26)); 20.9 (*t*, C(11)); 20.7 (*q*, C(19)); 18.7 (*q*, C(21)); 12.3 (*q*, C(18)). MS: *m/z* = 384 ($M^{+\cdot}$ -128 - 60, 1.6%), 368 (384 - 16, 4.3%). Anal. calc. for $C_{29}H_{49}IO_3$ (572.61): C 60.83, H 8.63; found: C 60.65, H 8.70.

Elution with toluene/Et_2O 8:2 gave 5α-cholestane-3α,5,6α-triol 3-acetate (**22**) (217 mg, 19.8%), m.p. 205 °C (from acetone -methanol). $[\alpha]_D^{25}$ = +31.0 (c = 1.0, $CHCl_3$). IR (KBr): 3484*s*, 3415*s*, 1739*s*, 1229*s*. ^{1}H-NMR (360 MHz): 0.65 (*s*, 3H, CH_3(18)); 0.87 (*d*, 6H, CH_3(26), CH_3(27)); 0.91 (*d*, 3H, CH_3(21)); 0.98 (*s*, 3H, CH_3(19)); 2.10 (*s*, 3H, AcO); 3.15 (*d*, 1H, *J* = 5.4 Hz, HO-C(3)); 3.25 (*s*, 1H, HO-C(5)); 4.12 (*m*, 1H, H-C(3)); 4.90 (*dd*, 1H, *J* = 12.5 Hz, 5.4 Hz, H-C(6)). ^{13}C-NMR: 170.6 (*s*, $CH_3\underline{C}OO$), 76.7 (*s*, C(5)), 74.1 (*d*, C(3)); 66.9 (*d*, C(6)), 56.2 (*d*, C(17)); 55.9 (*d*, C(14)); 44.6 (*d*, C(9)); 42.8 (*s*, C(13)); 40.6 (*s*, C(10)); 39.9 (*t*, C(12)); 39.5 (*t*, C(24)); 36.2 (*t*, C(22)); 35.8 (*d*, C(20)); 34.3 (*t*, C(4)); 33.7 (*d*, C(8)); 31.2 (*t*, C(2)); 28.7 (*t*, C(16)); 28.2 (*t*, C(7)); 28.0 (*d*, C(25)); 26.4 (*t*, C(1)); 24.0 (*t*, C(15)); 23.9 (*t*, C(23)), 22.8 (*q*, C(27)); 22.6 (*q*, C(26)); 21.2 (*q*, $\underline{C}H_3COO$)); 20.8 (*t*, C(11)); 18.7 (*q*, C(21)); 15.4 (*q*, C(19)); 12.1 (*q*, C(18)). MS: *m/z* = 426 ($M^{+\cdot}$ - 2x18, 7%), 402 ($M^{+\cdot}$ - 60, 36%), 384 ($M^{+\cdot}$ -60 - 18, 100%). Anal. calc. for $C_{29}H_{50}O_4$ (462.72): C 75.28, H 10.89; found: C 75.39, H 10.89.

Lithium aluminium hydride reduction of 6β-iodo-5α-hydroxycholestan-3-one acetate (**19**). - Compound **19** (110 mg) was reduced with $LiAlH_4$ (80 mg) in anh. Et_2O (10 mL) for 30 min. The residue obtained after the usual work up was chromatographed on silica gel (10 g). Toluene eluted cholest-5-en-3α-ol (4 mg, 5.4%), toluene/Et_2O 98:2 afforded cholest-5-en-3β-ol (29 mg, 38.9%), toluene/Et_2O 95:5 gave 5α-cholestane-3α,5-

-diol (16 mg, 20.5%), toluene/Et_2O 80:20 eluted 5α-cholestane-3β,5-diol (5 mg, 6.4%). IR and ^{1}H-NMR spectral characteristics of all the isolated products were identical to those of the corresponding authentic samples.

Epoxide ring closure in the iodohydrin **21**. - Iodohydrin **21** (50 mg) in MeOH (5 mL) was treated with 5% methanolic KOH solution (5mL) at room temperature for 2 h. The resulting mixture was concentrated *in vacuo* to a small volume and treated with water, affording as precipitate 5α,6α-epoxy-5α-cholestan-3α-ol (31 mg, 88.2%), m.p. 125-127 °C (from acetone-methanol; lit.[9] m.p. 125-128 °C).

Oxidation of cholest-5-en-3β-ol acetate (**11**) *with HgO/I_2. Procedure (i).* - A suspension of **11** (1.00 g, 2.33 mmol), HgO (4.04 g, 18.64 mmol) and I_2 (4.73 g, 18.64 mmol) in CCl_4 (400 mL) was irradiated for 4 h. The residue (2.1 g, obtained after the usual work up was recrystallyzed from $CHCl_3$/MeOH to give a ~1:1 mixture (695 mg, 67.0%) of 5,6α-epoxy-5α-cholestan-3β-ol acetate (**23a**) and 5,6β-epoxy-5β-cholestan-3β-ol acetate (**23b**) (estimated from the intensities of the signals for the C(6), C(18) and C(19) protons appearing in the ^{1}H-NMR spectrum of this mixture).

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component from cholesterol being 3β,5,6β-trihydroxy-5α-cholestane (isolated in 2 - 4% yield). Structure elucidation of **12**, **14a** and **14b**, mechanistic considerations of their formation, as well as X-ray analysis of **14b** were discussed in detail by these authors.[7]

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11. After 7 h irradiation, 10-15% of the starting product **9** was recovered by column chromatography.

12. Pathways d - f have been suggested by Suginome *et al.* to explain the formation of **12** and **14**.[7]

13. The yield refers to the crystalline product obtained by direct recrystallization of the crude reaction mixture. According to TLC, an additional amount of epoxides **23a** and **23b** was present in the mother liquor.

14. We wish to thank Dr. R. Tasovac (Microanalytical Laboratory, Faculty of Chemistry, Belgrade) for carrying out elemental microanalyses. Spectral determinations were performed (^{1}H-NMR and ^{13}C-NMR at 360 MHz) at Ciba-Geigy *Limited*, Basel, Switzerland (Dr. H. Fuhrer) and (IR and mass) in the laboratories for Instrumental Analysis, Faculty of Chemistry, Belgrade (direction Prof. D. Jeremić).

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