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# Synthesis of Some Five- and Six-Membered Oxasteroids of Cholestane Series by Ring Contraction and the Mass Spectrometric Fragmentations of Oxasteroids[1)]

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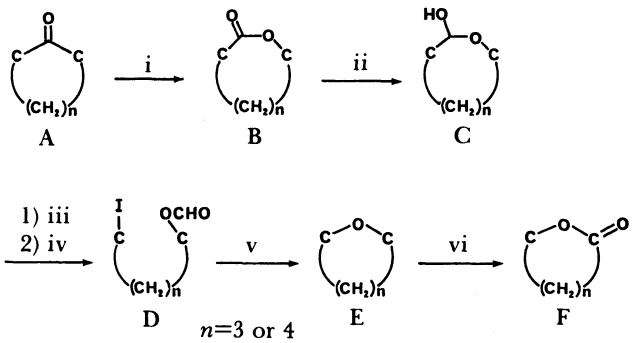
Synthesis of several new five- and six-membered oxasteroids of the cholestane series by the ring contraction of those oxasteroids whose oxygen-containing ring is larger by one member has been achieved. Ring contraction utilizes a series of reactions recently developed by us for the transformation of cyclic ketones into cyclic ethers; it involves a regioselective β-scission of the alkoxyl radical generated by irradiation of the lactol hypoiodite derived from the starting oxasteroid to give the iodoformate followed by its cyclization. The present work demonstrates the versatility of our new method for the synthesis of cyclic ethers and extends the scope of its application. The mass spectral fragmentation of some oxasteroids synthesized in the present and previous work is discussed.

We have recently reported a new, efficient and versatile method for transforming steroidal cyclic alcohols and ketones into cyclic ethers with the same ring size.[2-5)] The essential steps of the transformation of cyclic ketones into cyclic ethers are outlined as a sequence **A** to **E** in Scheme 1. The transformation involves four steps: a), the Baeyer-Villiger oxidation of cyclic ketones (**A**) to give the corresponding lactones (**B**); b), the reduction of these lactones with DIBAL (diisobutylaluminium hydride) to the corresponding lactols (**C**); c), a regioselective β-scission of the C-C bond of the corresponding hypoiodites generated in situ with mercury(II) oxide, iodine and pyridine, by irradiation to give an iodoformate (**D**); and d), the cyclization of the iodoformate to cyclic ether (**E**) with sodium borohydride or methyllithium.

By this method, a variety of steroidal ketones,[2,3)] camphor,[4)] and adamantanone[5)] have been transformed into the corresponding oxasteroids and cyclic ethers.

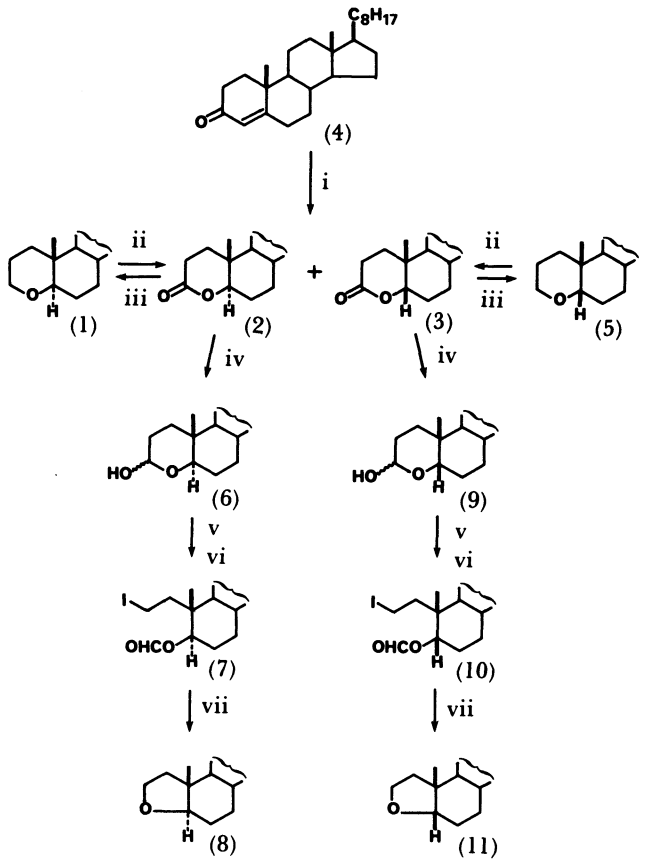
As will be apparent from Scheme 1, the oxasteroid (**E**) can be further transformed into oxasteroids with oxygen-containing rings smaller by one member if oxasteroid (**E**) can be oxidized to the corresponding lactone (**F**).




Scheme 1. Reagents: i, MCPBA: ii, DIBAL-toluene: iii, HgO-$I_2$-pyridine-benzene: iv, *hν*: v, MeLi-THF or $NaBH_4$-THF: vi, $RuO_2$-$NaIO_4$-$CCl_4$ or $CrO_3$-$CH_3CO_2H$-$H_2O$.

We therefore used this ring contraction sequence to undertake the synthesis of several more new five- and six-membered oxasteroids of the cholestane series in order to broaden the applicability of our method to include the synthesis of this group of chiral molecules of biological interest.

We chose three six-membered oxasteroids, 4-oxa-5α-cholestane (**1**),[3,6-9)] 4-oxa-5β-cholestane (**5**)[7)] and 4,4-




Scheme 2. Reagents: i, $K_2S_2O_8$-$H_2SO_4$-$CH_3COOH$: ii, $RuO_2$-$NaIO_4$-$CCl_4$: iii, $LiAlH_4$-$BF_3$-diethyl ether: iv, DIBAL-toluene: v, HgO-$I_2$-pyridine-benzene: vi, *hν*: vii, MeLi-THF.

dimethyl-3-oxa-5$\alpha$-cholestane (**12**)[2] and a seven-membered oxasteroid, 6-oxa-*B*-homo-5$\beta$-cholestane (**17**).[12]

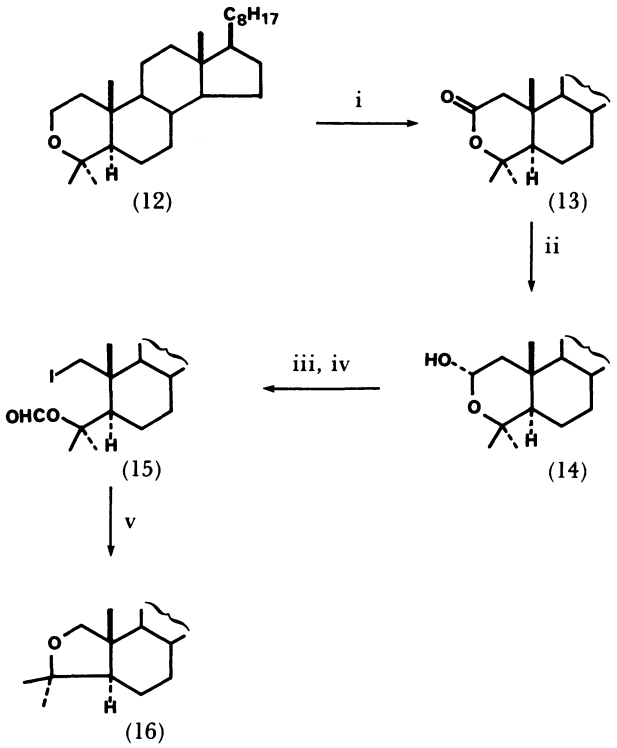
Oxidation of 4-oxa-5$\alpha$-cholestane (**1**) with ruthenium tetraoxide[10] in THF gave 4-oxa-5$\alpha$-cholestan-3-one (**2**)[7,9,11] in a good yield. Lactone **2** can be directly prepared by means of oxidation with peroxodisulfuric acid of cholest-4-en-3-one (**4**), as Pettit and Kasturi report.[9] Reduction of lactone **2** with DIBAL at $-78°C$ gave a mixture of the corresponding $\alpha$- and $\beta$-lactols **6**.[9] Irradiation of the hypoiodites of the lactol mixture generated in situ with mercury(II) oxide-iodine and pyridine in benzene with a Pyrex-filtered light readily gave an iodoformate **7**. Its cyclization to *A*-nor-3-oxa-5$\alpha$-cholestane (**8**) was achieved with methyllithium at $-78°C$ in an almost quantitative yield.

The isomeric 4-oxa-5$\beta$-chloestane (**5**), prepared after Edward and Morand,[7] was similarly oxidized to give 4-oxa-5$\beta$-cholestan-3-one (**3**)[7,11] with ruthenium tetraoxide (84%). Lactone **3** was then successively transformed into the lactols **9** (81%) and iodoformate **10** (59%). The cyclization of **10** with $NaBH_4$ gave *A*-nor-3-oxa-5$\beta$-cholestane (**11**). In the course of our study of the oxidation of cholest-4-en-3-one (**4**) with peroxodisulfuric acid after Pettit and Kasturi,[9] we found that lactone **3** can be obtained as a by-product (8% yield) along with the isomeric 5$\alpha$-lactone **2**[7,9,11] (32% yield) reported by them. Although the yield is low, the formation of lactone **3** by one step from a readily available cholest-4-en-3-one may be useful in bringing about a quicker synthesis of lactone **3**.

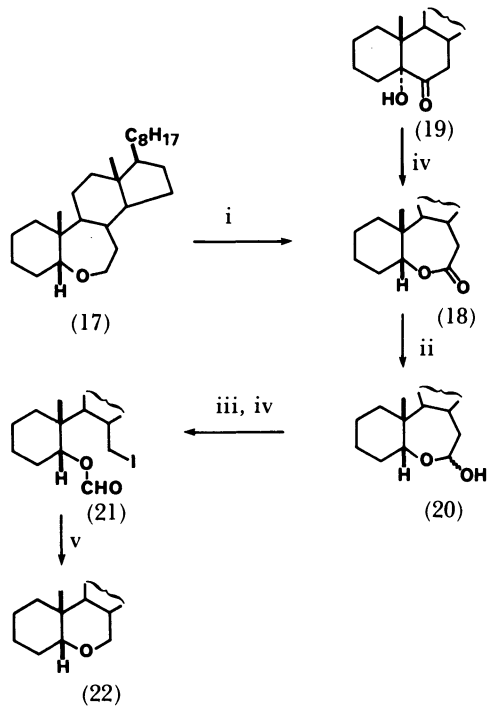
We were also able to transform 4,4-dimethyl-3-oxa-5$\alpha$-cholestane (**12**)[2] into 3,3-dimethyl-*A*-nor-2-oxa-5$\alpha$-cholestane (**16**) through a lactone **13**, an $\alpha$-lactol **14**, and an iodoformate **15** in a good overall yield (Scheme 3).

We then turned our attention to the preparation of six-membered oxasteroids. Oxidation of *B*-homo-6-oxa-5$\beta$-cholestane (**17**)[12] with ruthenium tetraoxide in THF gave *B*-homo-6-oxa-5$\beta$-cholestan-6-one (**18**) in an 88% yield. This new lactone was also prepared by stereospecific photo-rearrangement of 5-hydroxy-5$\alpha$-cholestan-6-one (**19**)[13] according to the method reported by Cookson et al.[14] Reduction of lactone (**18**) with DIBAL gave a mixture of *B*-homo-6-oxa-5$\beta$-cholestan-7$\alpha$- and 7$\beta$-ols **20** in a 90% yield. Preparation of the corresponding hypoiodites with mercury(II) oxide, iodine and pyridine in benzene followed by the irradiation of the solution gave an iodoformate **21** in a 45% yield. Its cyclization with methyllithium gave a new oxasteroid, 6-oxa-5$\beta$-cholestane (**22**) in an 87% yield (Scheme 4).

The present results broaden the applicability of our method for the transformation of cyclic ketones into cyclic ethers and will extend its scope for application to synthetic problems. It should also be noted that since we have recently shown that the iodoformates in the sequence outlined in Scheme 1 can be transformed into thia- and azasteroids,[15] the present results imply




Scheme 3. Reagents i, $CrO_3CO_2H$-$H_2O$: ii, DINBAL-toluene: iii, HgO-$I_2$-pyridine-benzene: iv, $h\nu$: v, MeLi-THF.




Scheme 4. Reagents: i, $RuO_2$-$NaIO_4$-$CCl_4$: ii, DIBAL-toluene: iii, HgO-$I_2$-pyridine-benzene: iv, $h\nu$: v, MeLi-THF.

that the transformation of 6- or 7-membered oxasteroids into 5- or 6-membered cyclic sulfides as well as amines is now achievable.

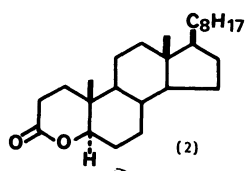
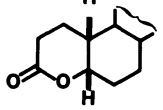
**The Mass Spectrometric Fragmentations of the Oxasteroids.** The synthesis of a number of oxasteroids, steroidal lactones, and steroidal lactols reported in previous papers[2,3] as well as in the present ones has provided us with a good opportunity to examine the pattern of their mass spectral fragmentations.

In the following part, the structures and the probable genesis of the major fragment ions in the mass spectra of steroidal lactones, lactols, and cyclic ethers described in this and the previous papers,[2,3] are briefly discussed.

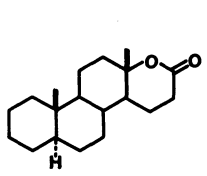
a) **Steroidal Lactones.** The mass spectral fragmentation of certain steroidal lactones has already been reported.[16] Our studies have revealed that the lactone-directed fragmentation and the general fragmentation of a complex hydrocarbon framework take place competitively after the electron impact of steroidal lactones.

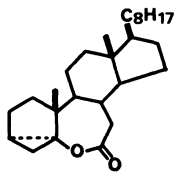
We examined the mass spectra of four lactones **2**, **3**, **13**, and **18**, prepared in the present work, as well as the mass spectra of four lactones, 17*a*-oxa-*D*-homo-5*α*-androstan-17-one (**23**), 3*α*,5-cyclo-6-oxa-*B*-homo-5*α*-cholestan-7-one (**24**), 7*a*-oxa-*B*-homo-5*α*-cholestan-7-one (**25**), and 6-oxa-*B*-homo-5*α*-cholestan-7-one (**26**) reported in our previous paper.[3] We found that the mass spectra of these 8 lactones can be divided into two categories according to their mode of fragmentation. Thus, the mass spectra of lactones **2** and **3** are grouped in a category that exhibits a fragmentation pattern similar to that of the corresponding steroidal hydrocarbons. One of the distinct features of the mass spectra of the C-17 substituted steroidal hydrocarbons is the expulsion of the ring-D; this is of diagnostic importance. The genesis of this expulsion that involves both single and reciprocal electron transfers has been established by Djerassi and his colleagues.[16,17] The intensities of the molecular ions and fragment ions that arise from the ring-D cleavage of lactones **2** and **3** are listed in Table 1. Although no appreciable ions arising from the fragmentation of the oxygen-containing A-rings are present in the mass spectra of lactones **2** and **3**, the comparison of the mass spectra of the two isomeric lactones shows an interesting difference in the intensities of the fragment ions that arise from their ring-D cleavage. Thus, while the intensity of the fragment ions corresponding to the elimination of the ring-D involving both a single electron transfer and a reciprocal electron transfer were 100 and 70%, the intensity of the fragment ions corresponding to the elimination of the ring-D of the mass spectrum of the isomer was only 14 and 11%. It is thus apparent that the geometry of the remote ring can exert an appreciable effect on the elimination of the ring-D of these isomeric steroids during the electron impact.

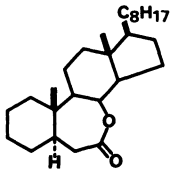
Table 1. Intensities of the Molecular Ions and the Fragment Ions Corresponding to the Elimination of the Ring-D of Isomeric Lactones **2** and **3**

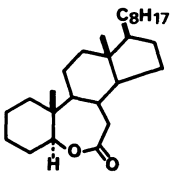
| Lactone | M+ ion/% | M+−155 ion/% | M+−154 ion/% |
|---|---|---|---|
|  (2) | 72 | 100 | 70 |
|  (3) | 100 | 14 | 11 |

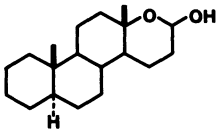
This seems to be a clear example of "conformational transmission"[18] in the mass spectrometric fragmentation. The mass spectra of the six other lactones revealed lactone-directed fragmentation. Thus, lactone **13** exhibited the fragment ion of *m/z* 316 that arose from the elimination of the ring-A as the base peak while the parent ion was very weak (2%). Accurate mass measurement indicated that the elemental composition of the ion at *m/z* 316 is $C_{23}H_{40}^+$ (316.31407). The probable structure of the ion

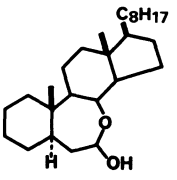

(23)

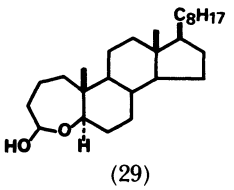

(24)

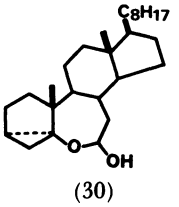

(25)


(26)


(27)


(28)


(29)


(30)

together with its genesis is outlined in Scheme 5.

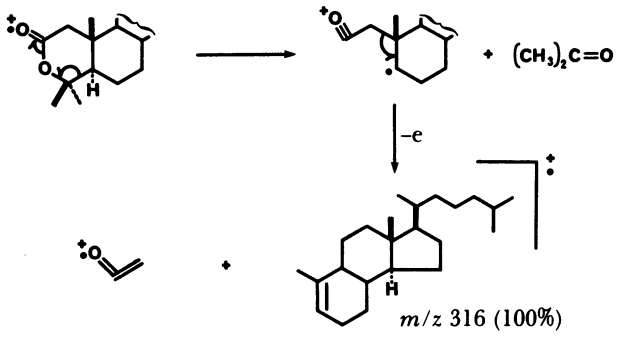
The mass spectrum of lactone **23**[3] exhibited a fragment ion at $m/z$ 218 as the base peak and an oxonium ion at $m/z$ 275 (32%) arising from the expulsion of 13$\beta$-Me from the molecular ion (Scheme 6). The intensity of the oxonium ion at $m/z$ 275 was only 32% and this low intensity contrasts with the ion that arises from the expulsion of 13$\alpha$-Me in the mass spectrum of a 17-oxasteroid,[19] which has been reported to be very prominent. Accurate mass measurement showed that the elemental composition of the base peak is $C_{16}H_{26}^+$ (218.20296). A probable structure of the ion at $m/z$ 218 and its genesis involving the elimination of the ring-D is outlined in Schceme 7.

The mass spectra of isomeric seven-membered lactones **18** and **26** exhibited almost identical patterns of fragmentation, with a fragment ion at $m/z$ 318 as their base peak. Accurate mass measurement of the ion that arises from lactone **18** indicated that the elemental composition of the ion is $C_{22}H_{38}O^+$ (318.29253). Scheme 8 illustrates a probable structure of the ion and its genesis.

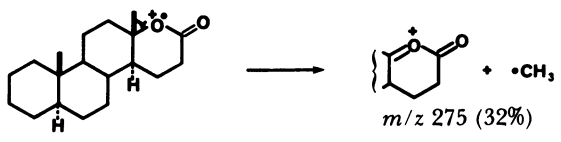
Although lactone **24** is structurally analogous to lactones **18** and **26**, its mass spectral fragmentation, nevertheless differed considerably from those of lactones **18** and **26**. It showed an ion at $m/z$ 95 as the base peak and the intense ion at $m/z$ 400 ($M^+ - CO$, 54.9%). A probable genesis of the ion at $m/z$ 95, which was proved to have the elemental composition $C_7H_{11}^+$ by accurate mass measurement, is outlined in Scheme 9. An ion at $m/z$ 95 was again the base peak in the mass spectrum of lactones **25**. A probable structure and the genesis of the ion is outlined in Scheme 10.

b) **Steroidal Lactols.** We examined the mass spectra of seven steroidal lactols, 17*a*-oxa-*D*-homo-5$\alpha$-androstan-17$\alpha$- and 17$\beta$-ols (**27**), 7*a*-oxa-*B*-homo-5$\alpha$-cholestan-7$\alpha$- and 7$\beta$-ols (**28**), 4*a*-oxa-*A*-homo-5$\alpha$-cholestan-4$\alpha$- and 4$\beta$-ols (**29**), 3$\alpha$,5-cyclo-6-oxa-*B*-homo-5$\alpha$-cholestan-7$\alpha$- and 7$\beta$-ols (**30**), 4-oxa- 5$\alpha$- and 5$\beta$-cholestan-3$\alpha$- and 3$\beta$-ols (**6**) and (**9**), and 4,4-dimethyl-3-oxa-5$\alpha$-cholestan-2$\alpha$-ol (**14**). Most of these lactols showed that the decomposition of their oxygen-containing ring is predominant over the decomposition of their hydrocarbon framework. Thus, the mass spectrum of lactol **27** exhibited the base peak at $m/z$ 218; this is equivalent to the ion from the corresponding lactone **23** (Scheme 7), which is attributable to the ion arising from the expulsion of the ring-D.

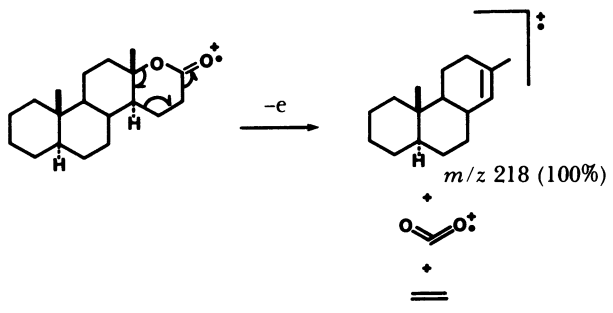
The mass spectrum of steroidal lactol **28** exhibited the base peak at $m/z$ 95. Accurate mass measurement indicated that its elemental composition was $C_7H_{11}^+$ (95.0858). The ion probably arises from the breakdown of the oxygen-containing ring as outlined in



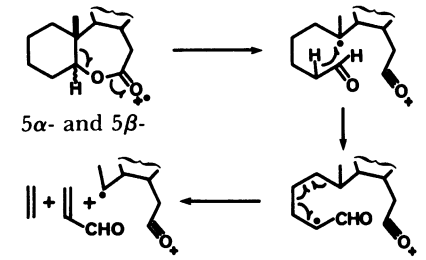

Scheme 5.



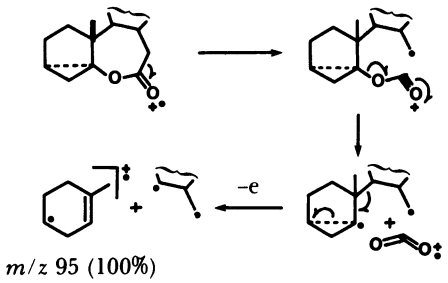

Scheme 6.



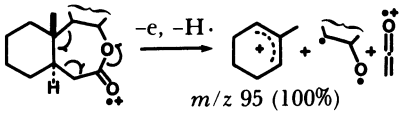

Scheme 7.




Scheme 8.




Scheme 9.

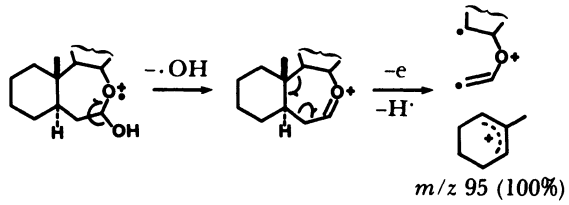



Scheme 10.

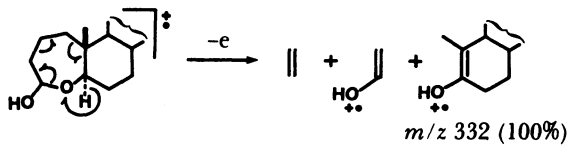
Scheme 11.

The base peak in the mass spectrum of steroidal lactol **29** appeared at $m/z$ 332. Accurate mass measurement indicated that the elemental composition was $C_{23}H_{40}O^+$ (332.3092). The outline formation of this ion is rationalized in Scheme 12. It can be formed by the loss of the ring-A with a transfer of the angular hydrogen to the ethereal oxygen.

The mass spectrum of lactol **30** exhibited the base peak at $m/z$ 111. Accurate mass measurement indicated that the elemental composition was $C_7H_{11}O^+$ ($m/z$ 111.0826). The genesis of this ion, which involved a breakdown of its oxygen-containing ring, is outlined in Scheme 13.

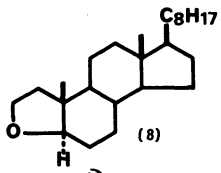
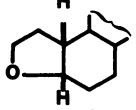
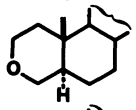
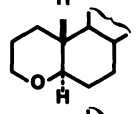
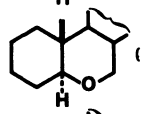
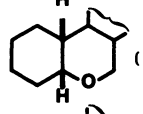
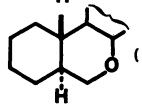



Scheme 11.




Scheme 12.

Table 2. Intensities of the Molecular Ion and the Fragment Ions Corresponding to the Elimination of the Ring-D of Some Oxasteroids of Cholestane Series

| Substrate | M+ ion/% | M+−155 ion/% | M+−154 ion/% |
|---|---|---|---|
|  (8) | 75 | 100 | 74 |
|  (11) | 100 | 13 | 16 |
|  (31) | 79 | 100 | 76 |
|  (1) | 54 | 100 | 48 |
|  (32) | 37 | 100 | 28 |
|  (22) | 36 | 100 | 20 |
|  (33) | 7 | 100 | 6 |

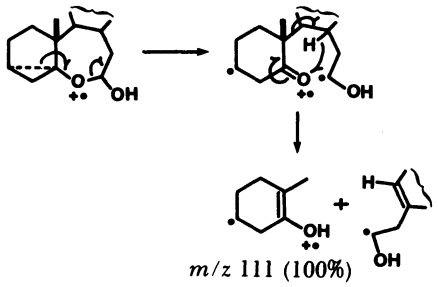
The mass spectra of isomeric lactols **6** and **9** both exhibited their base peaks at $m/z$ 372, owing to a loss of water.

Finally, the mass spectrum of 4,4-dimethyl-3-oxa-5$\alpha$-cholestan-2-ol (**14**) exhibited the base peak at $m/z$ 385; this is assignable to the loss of the element of water and the 4-methyl group.

c) **Steroidal Ethers.** We examined the mass spectra of 12 steroidal cyclic ethers prepared in our present and the previous work. As in the case of the steroidal lactones the mass spectra of these cyclic ethers can be divided into two categories according to their type of the fragmentation.

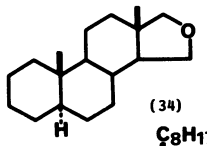
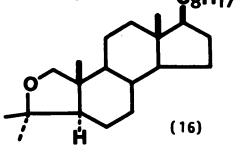
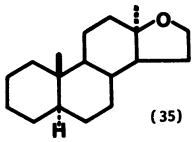
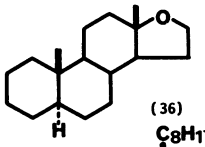
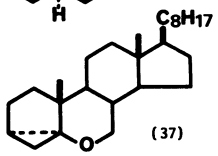
The mass spectra of seven steroidal cyclic ethers listed in Table 2 are grouped in the first category which shows fragmentation similar to that of the steroidal hydrocarbons. The mass spectra of these oxasteroids with an oxygen atom in their ring-A or B showed, with only one exception, normal fragmentation arising from the elimination of their ring-D. The mass spectrum of *A*-nor-3-oxa-5$\beta$-cholestane (**11**) showed the molecular ion as the base peak while the intensity of the fragment ions that corresponded to the elimination of the ring-D with a single electron transfer and a reciprocal electron transfer were only 13 and 16%. The 5$\alpha$-isomer **8**, on the other hand, gave the mass 205 ion as the base peak and the ion at $m/z$ 206 was very intense (74%). This is another example of what has been called the "conformational transmission" in the mass spectrometric fragmentation which we have already found in the mass spectra of the isomeric pair of lactones **2** and **3**. The geometry of the remote ring exerts a notable effect on the elimination of the ring-D of these oxasteroids during the electron impact.

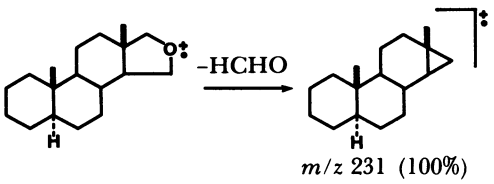
The mass spectra of the five further oxasteroids listed in Table 3 exhibited fragmentation directed by their oxygen-containing ring. The mass spectrum of 16-oxa-5$\alpha$-androstane (**34**) exhibited its base peak at $m/z$ 231. The probable genesis, which is based on an




Scheme 13.

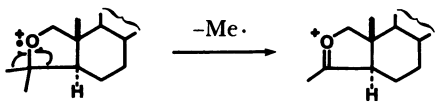
Table 3. The Base Peak and the Intensities of the Molecular Ions of Some Oxasteroids

| Substrate | $M^+$ ion/% | $M^+-155$ ion/% | $M^+-154$ ion/% |
|---|---|---|---|
|  (34) | 10 | — | 100 |
|  (16) | 0.4 | 85 | 100 |
|  (35) | 0.2 | 100 | — |
|  (36) | 1.5 | 100 | — |
|  (37) | 100 | — | *m/z* 111 (89%) |

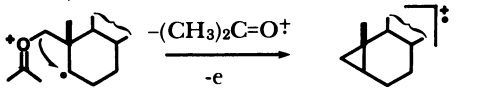


*m/z* 231 (100%)

Scheme 14.

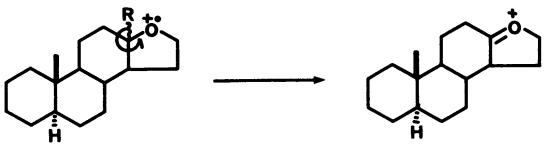


*m/z* 373 (85%)



*m/z* 330 (100%)

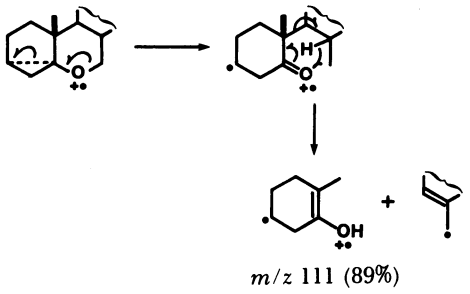
Scheme 15.



R=α- and β-Me

*m/z* 247 (100%)

Scheme 16.



*m/z* 111 (89%)

Scheme 17.

analogy with the loss of formaldehyde from tetrahydrofuran, [20] is outlined in Scheme 14.

The mass spectrum of 3,3-dimethyl-2-oxa-*A*-nor-5α-cholestane (**16**) exhibited the base peak at *m/z* 330 and an intense fragment ion at *m/z* 373 (85%). The base peak arises as the result of a similar loss of the element of acetone while the latter is generated by the expulsion of the 3-methyl-group as outlined in Scheme 15.

The mass spectra of 17-oxa-5α-androstane (**35**) and its 13-epimer (**36**) exhibited their base peak at *m/z* 247; this arises from the expulsion of 13α- and 13β-methyl group, as expected (Scheme 16).

The mass spectrum of 3α,5-cyclo-6-oxa-5α-cholestane (**37**) exhibited the molecular ion as the base peak and an intense fragment ion at *m/z* 111 (89%). Accurate mass measurement indicated that the molecular composition of the latter was $C_7H_{11}O^+$ (*m/z* 111.0828). Its formation is rationalized as outlined in Scheme 17.

## Experimental

Mps were recorded with a Yanagimoto micro mp apparatus. IR spectra were determined for Nujol mulls with a Hitachi Model 285 infrared spectrophotometer. $^1H$ NMR spectra were determined with a JEOL PS 200 high-resolution FT-NMR spectrometer (200 MHz) (Solvent, $CDCl_3$: $SiMe_4$ as an internal standard) (Faculty of Pharmaceutical Sciences of this University). TLC was carried out on a Merck Kiesel gel 60 $PF_{254}$. All the high and low resolution mass spectra were recorded with a JEOL JMS-D 300 spectrometer (70 eV) (Faculty of Agriculture). Elemental analysis was performed by the staff of the Laboratory for Microanalysis of the Faculty of Pharmaceutical Sciences of this University.

**4-Oxa-5α-cholestan-3-one (2).** An aqueous $NaIO_4$ solution (300 mg $NaIO_4$ in water 1 ml) was added dropwise to carbon tetrachloride (4 ml) containing $RuO_2 \cdot X\,H_2O$ (15 mg) while stirring at about 0°C. 4-Oxa-5α-cholestane (**1**)[3,6-9] (65 mg) in carbon tetrachloride (4 ml) was added dropwise at room temperature to the solution containing $RuO_2$. The solution was stirred for 4 h and a further amount of aq $NaIO_4$ solution (100 mg $NaIO_4$ in water 0.3 ml) was added. The solution was stirred 20 h. After the addition of isopropyl alcohol to the solution, $RuO_2$ was removed by filtration. The solution was washed with water and dried over anhydrous $Na_2SO_4$. The work-up as usual gave crystals (60 mg) which were subjected to preparative TLC with

a 5 : 1 mixture of benzene and diethyl ether. Two fractions were obtained. The more mobile TLC fraction (13 mg) was the starting material. The less mobile fraction (35 mg, 65% based on the converted material) was lactone **2** which was recrystallized from pet. ether. Mp 111—118°C (lit,[7] mp 114—115°C; lit,[9] mp 118—119°C; lit,[11] mp 116—116.5°C). $^1$H NMR (90 MHz) $\delta$=0.67 (3H, s, 18-H), 0.93 (3H, s, 19-H), 3.95 (1H, dd, $J$=11.20 and 4.61 Hz, 5$\alpha$-H), and 2.55—2.68 (2H, m, 2-H), MS $m/z$ (rel intensities) 388 ($M^+$, 72%), 233 (100), 81 (48), 55 (60), and 43 (97).

**4-Oxa-5$\alpha$-cholestan-3-ols (6).**[9] A solution of DIBAL (1.8 ml) was added dropwise to a solution of the lactone **2** (570 mg) in dry toluene (40 ml) at −78°C. The solution was stirred for 3 h at −78°C and poured into iced water. After the solution had been filtered, the filtrate was extracted with dichloromethane. The organic layer was washed with water and dried over anhydrous $Na_2SO_4$. The usual work-up gave a product (540 mg) which was recrystallized from acetone-dichloromethane to yield a 1 : 1 mixture of $\alpha$- and $\beta$-lactols **6**, mp 185—187°C (lit,[9] $\beta$-lactol, 197—199°C). $^1$H NMR $\delta$=0.65 (3H, s, 18-H of $\alpha$- and $\beta$-ols), 0.91 and 0.94 (each s, 19-H of $\alpha$- and $\beta$-ols), 3.01 (dd, $J$=11.23 and 4.40 Hz, 5$\alpha$-H of 3$\beta$-ol), 3.71 ($J$=10.74 and 5.37 Hz, 5$\alpha$-H of 3$\alpha$-ol), 4.73 (m, 3$\alpha$-H of 3$\beta$-ol), and 5.25 (m, 3$\beta$-H of 3$\alpha$-ol), MS, $m/z$ (rel intensity) 390 ($M^+$, 0.5%), 372 [$(M-H_2O)^+$, 100], and 83 (83).

**Irradiation of the Hypoiodite of 4-Oxa-5$\alpha$-cholestan-3-ols in the Presence of Mercury(II) Oxide and Iodine.** Lactols **6** (300 mg) were added to dry benzene (39 ml) containing pyridine (0.5 ml), mercury(II) oxide (332 mg), and iodine (391 mg). The solution in a Pyrex vessel was irradiated for 2 h in an atmosphere of nitrogen. The solution was filtered and the filtrate was worked up as usual to give an oily product (419 mg) which was subjected to preparative TLC with benzene. Three fractions were obtained. The most mobile TLC fraction (200 mg) was crystalline formate **7**. The next fraction (17 mg) was an intractable mixture. The least mobile fraction (120 mg) was lactone **2**. The formate **7** was recrystallized from methanol-acetone. Mp 99 — 100°C. (Found: C, 60.42; H, 8.76 %. Calcd for $C_{26}H_{45}IO_2$: C, 60.46; H, 8.78%). IR 1718 (CHO), 1210 and 1183 cm$^{-1}$ (OCHO), $^1$H NMR $\delta$=0.65 (3H, s, 18-H), 0.92 (3H, s, 19-H), 2.95—3.19 (2H, m, 2-H), 4.86 (1H, dd, $J$ = 11.23 and 4.89 Hz, 5$\alpha$-H), 8.10 (1H, s, OCHO); MS $m/z$ (rel intensity) 516 ($M^+$, 0.4%), 470 [$(M-OCH_2O)^+$, 8.2], 389 [$(M-I)^+$, 31], 343 (53), 315 (39), 287 (62), and 55 (100).

**3-Oxa-A-nor-5$\alpha$-cholestane (8).** A solution of formate **7** (140 mg) in THF (30 ml) was cooled to −78°C by Dry Ice-methanol. Methyllithium (1.05 M† diethyl ether solution) (0.7 ml) was added to this stirred solution. The solution was stirred for 30 min at that temperature and then stirred for further 1 h at room temperature and then extracted with diethyl ether. The ethereal solution was worked up as usual. A crystalline product (98 mg) was recrystallized from methanol-acetone to yield a pure specimen (89 mg), mp 77—78°C. (Found: C, 83.11; H, 12.42%. Calcd for $C_{25}H_{44}O$: C, 83.27; H, 12.30%). IR 1124, 1010, and 975 cm$^{-1}$; $^1$H NMR $\delta$=0.67 (3H, s, 18-H), 0.81 (3H, s, 19-H), 3.04 (1H, dd, $J$=12.21 and 3.91 Hz, 5$\alpha$-H), 3.85—3.93 (2H, m, 2-H); MS $m/z$ (rel intensity) 360 ($M^+$, 75%), 345 [$(M-Me)^+$, 35], and 205 (100).

**Oxidation of Cholest-4-en-3-one with Peroxodisulfuric Acid.** Potassium peroxodisulfate (3 g) and concd sulfuric acid (3.3 g) were dissolved in glacial acetic acid (50 ml). The mixture was added to a solution of cholest-4-en-3-one (3 g) in glacial acetic acid (50 ml). The solution was stirred for two weeks at room temperature in the absence of light. The mixture was treated with aqueous 50% potassium hydroxide (14 ml). Precipitated salts were removed by filtration and the filtrates evaporated. The residue was extracted with diethyl ether. The ether solution was washed with water and dried over anhydrous $Na_2SO_4$. The solution was worked up as usual. The product (2.5 g) was subjected to column chromatography (Merck Kiesel gel 60; 70—230 mesh, 40 g). Elutions with benzene gave a major fraction (1.38 g) which was a crystalline mixture of lactones. Recrystallization with pet. ether gave 4-oxa-5$\alpha$-cholestan-3-one (620 mg). The filtrate of the recrystallization was evaporated to yield a mixture of 5$\alpha$- and 5$\beta$-lactones. An attempted separation of the mixture to its two components by preparative TLC with a variety of solvents was unsuccessful. The mixture was therefore subjected to fractional crystallization with methanol-pet. ether 6 times to give almost pure 5$\beta$-lactone **3**, (40 mg). This lactone was subjected to DIBAL reduction. A pure lactone melted at 106 — 107°C (pet. ether) (lit,[11] 109.5 — 110°C, lit,[7] 107 — 107.5°C). $^1$H NMR $\delta$=0.68 (3H, s, 18-H), 0.99 (3H, s, 19-H), 2.39—2.56 (2H, m, 2-H), and 4.14 (1H, dd, $J$=3.3 and 2.4 Hz), MS $m/z$ (rel intensity) 388 ($M^+$, 100%), 315 (6), 233 (14), and 55 (19).

**Reduction of 4-Oxa-5$\beta$-cholestan-3-one.** Lactone **3** (38 mg) was dissolved in dry toluene (5 ml) and the solution was cooled to −78°C by Dry Ice-methanol. A DIBAL solution (0.13 ml) was added to this solution and the solution was stirred for 2 h at −78°C. The solution was poured into water and the inorganic precipitates were removed by filtration. The solution was washed with water and dried. The usual work-up gave 4-oxa-5$\beta$-cholestan-3-ols (40 mg) which were purified by preparative TLC with a 5 : 1 benzene-diethyl ether to yield an oily mixture of 4-oxa-5$\beta$-cholestan-3$\alpha$- and 3$\beta$-ols. (Found: $m/z$ 390.3533. Calcd for $C_{26}H_{46}O_2$: M, 390.3498). IR (neat) 3365 (OH) and 1015 cm$^{-1}$; $^1$H NMR $\delta$=0.65 (3H, s, 18-H of 3$\alpha$- and 3$\beta$-ols), 0.88 and 0.92 (each 3H, each s, 19-H of 3$\alpha$- and 3$\beta$-ols), 3.30 and 3.84 (each 1H, each, brs, 5$\beta$-H of 3$\alpha$- and 3$\beta$-ols), and 4.72 and 5.32 (each 1H, each brs, 3$\alpha$- and 3$\beta$-H of 3$\alpha$- and 3$\beta$-ols); MS $m/z$ (rel intensity) 390 ($M^+$, 7%), 372 [$(M-H_2O)^+$, 100], and 315 (14).

**Irradiation of the Hypoiodite of 4-Oxa-5$\beta$-cholestan-3-ols in the Presence of Mercury(II) Oxide and Iodine.** Lactols **9** (68 mg) were added to a dry benzene (9 ml) containing pyridine (0.1 ml), mercury(II) oxide (75 mg) and iodine (89 mg). The solution in a Pyrex vessel was irradiated for 2 h in an atmosphere of nitrogen. The solution was filtered and the filtrate was worked up as usual to give a crystalline product (98 mg) which was subjected to preparative TLC with benzene. Of the two fractions, the more mobile TLC fraction was a crystalline formate **10** (53 mg). After recrystallization from acetone-methanol, the formate melted at 112 — 117°C. (Found: $m/z$ 516.2490. Calcd for $C_{26}H_{45}IO_2$: M, 516.2465). IR (Nujol) 1728 (CHO) and

† 1M=1 mol dm$^{-3}$.

1190 $cm^{-1}$ (OCHO); $^1H$ NMR $\delta$= 0.66 (3H, s, 18-H), 0.95 (3H, s, 19-H), 3.00—3.15 (2H, m, $-CH_2I$), 4.88 (1H, br. s, 5 $\beta$-H) and 8.11 (1H, s, CHO); MS *m/z* (rel intensity) 516 ($M^+$, 0.7%), 470 [$(M-OCH_2O)^+$, 14], 389 [$(M-I)^+$, 48], and 343 [$(M-OCH_2O-I)^+$, 100].

**3-Oxa-*A*-nor-5$\beta$-cholestane (11).** A solution of formate **10** (51 mg) in THF (10 ml) was cooled to −78°C. To this stirred solution, there was added methyllithium (1.05 M diethyl ether solution) (0.24 ml). The solution was stirred for 30 min and then the temperature of the solution was raised to room temperature. The solution was stirred for 1 h at room temperature and extracted with diethyl ether. The usual work-up of the solution gave a crude crystalline oxasteroid **11**. This was then recrystallized from methanol-acetone. Mp 91.5—92.5°C. (Found: C, 83.09; H, 12.31%. Calcd for $C_{25}H_{44}O$: C, 83.27; H, 12.30%). IR (Nujol) 1039 and 1017 $cm^{-1}$ (C-O); $^1H$ NMR $\delta$= 0.67 (3H, s, 18-H), 0.93 (3H, s, 19-H), 3.43 (1H, dd, $J$= 2.9 and 2.4 Hz, 5$\beta$-H), and 3.75—3.94 (2H, m, 2-H), MS *m/z* (rel intensity) 360 ($M^+$, 100%), 345 [$(M-Me)^+$, 3], 315 (6), 206 (16), and 43 (34).

**4,4-Dimethyl-3-oxa-5$\alpha$-cholestan-2-one (13).** A solution of aqueous acetic acid (0.5 ml of water plus 5 ml of acetic acid) containing chromium trioxide (200 mg) was added dropwise to an acetic acid solution (10 ml) of 4,4-dimethyl-3-oxa-5$\alpha$-cholestane (103 mg) at room temperature. The solution was stirred overnight and then heated at 40°C for 2 h. The solution was extracted with dichloromethane and the organic layer was neutralized with aqueous sodium hydrogencarbonate. The usual work-up of the solution gave an oily product which was subjected to preparative TLC to give a crystalline lactone **13** (35 mg). This was recrystallized from acetone-methanol to yield a pure material, mp 171—173°C. (Found: C, 80.62; H, 11.60%. Calcd for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61%). IR 1720 (C=O), 1114, 1100, 989, and 950 $cm^{-1}$; $^1H$ NMR $\delta$= 0.65 (3H, s, 18-H), 1.00 (3H, s, 19-H), 1.34 and 1.40 (each 3H, each s, *gem* dimethyl), and 1.92 and 2.65 (each 1H, each d, $J$= 16.8 Hz, 1-H), MS *m/z* (rel intensity) 416 ($M^+$, 2%), 401 [$(M-Me)^+$, 1.5], 358 (1.5), and 316 [(M−ring-A)$^+$, 100].

**4,4-Dimethyl-3-oxa-5$\alpha$-cholestan-2$\alpha$-ol (14).** A solution of DIBAL (0.1 ml) was added dropwise to a solution of lactone **13** (31 mg) in dry toluene (5 ml) at −78°C. The solution was stirred for 3 h and poured into iced water. After the solution was filtered, the solution was washed with water and dried over anhydrous $Na_2SO_4$. The work-up by the usual method gave a product (32 mg) which was recrystallized from acetone to yield 2$\alpha$-lactol **14**. Mp 166—170°C. (Found: C, 80.07; H, 12.05%. Calcd for $C_{28}H_{50}O_2$: C, 80.32; H, 12.04%). IR 3375 (OH), 1130, and 1048 $cm^{-1}$ (C-O); $^1H$ NMR $\delta$=0.63 (3H, s, 18-H), 1.01 (3H, s, 19-H,), 1.18 and 1.24 (each 3H, each s, *gem* dimethyl), 2.75 (1H, d, $J$=7.3 Hz, OH), and 5.06 (1H, ddd, $J$=9.0, 7.3, and 2.0 Hz, 2$\beta$-H); MS *m/z* (rel intensity) 400 [$(M-H_2O)^+$, 9%], 385 [$(M-H_2O-Me)^+$, 100], 316 (51), 95 (35), and 43 (94).

**Irradiation of the Hypoiodite of 4,4-Dimethyl-3-oxa-5$\alpha$-cholestan-2$\alpha$-ol (14).** The lactol (14 mg) was added to a dry benzene (3 ml) containing pyridine (0.05 ml), mercury(II) oxide (15 mg) and iodine (17 mg). The solution in a Pyrex vessel was irradiated for 2 h in an atmosphere of nitrogen. The solution was filtered and the filtrate was worked up as usual to give oily formate (20 mg). The product was subjected to preparative TLC with benzene. Of the two fractions, the more mobile TLC fraction was an oily formate **15** (11 mg). (Found: *m/z* 417.3760. Calcd for $C_{28}H_{49}IO_2-I$: M, 417.3732). IR (neat) 1720 (CHO), 1180 and 1143 $cm^{-1}$ (OCHO); $^1H$ NMR $\delta$=0.63 (3H, s, 18-H), 1.13 (3H, s, 19-H), 1.56 and 1.63 (each 3H, each s, *gem* dimethyl), 3.35 and 3.94 (each 1H, each d, $J$=10.25 Hz, $CH_2I$), and 8.12 (1H, s, CHO); MS *m/z* (rel intensity) 417 [$(M-I)^+$, 0.8%], 371 [$(M-I-OCH_2O)^+$, 81], 301 (18), and 95 (100).

**3,3-Dimethyl-*A*-nor-2-oxa-5$\alpha$-cholestane (16).** A solution of formate **15** (10 mg) in THF (3 ml) was cooled to −78°C. To this stirred solution, there was added methyllithium (0.57 M diethyl ether solution) (0.08 ml). The solution was stirred for 1 h at that temperature and thereafter stirred for further 1 h at room temperature and extracted with diethyl ether. The usual work-up of the solution gave an almost pure crystalline oxasteroid **16** (7 mg). It was recrystallized from methanol. Mp 106—107°C. (Found: C, 83.21; H, 12.38%. Calcd for $C_{27}H_{48}O_2$: C, 83.43; H, 12.45%). IR 1019 and 1014 $cm^{-1}$ (C-O); $^1H$ NMR $\delta$=0.66 (3H, s, 18-H), 1.01 (3H, s, 19-H), 1.13 and 1.19 (each 3H, each s, *gem* dimethyl), 3.27 and 3.58 (each 1H, each d, $J$= 7.33 Hz, 1H), MS *m/z* (rel intensity) 388 ($M^+$, 0.4%), 373 [$(M-Me)^+$, 85], 330 [$(M-(CH_3)_2CO)^+$, 100], 288 (39), 217 (38), 175 (34), 95 (38), and 43 (42).

***B*-Homo-6-oxa-5$\beta$-cholestan-7-one (18).** Aqueous $NaIO_4$ solution (200 mg $NaIO_4$ in water 1 ml) was added dropwise to carbon tetrachloride (3 ml) containing $RuO_2 \cdot X\,H_2O$ (20 mg) while stirring at about 0°C . The *B*-homo-6-oxacholestane (**17**) (23 mg) in carbon tetrachloride (3 ml) was added dropwise to the solution containing ruthenium tetraoxide at 0°C. The solution was stirred for 5 h at room temperature. After the addition of isopropyl alcohol to the solution, $RuO_2$ was removed by filtration. The solution was washed with water and dried over anhydrous $Na_2SO_4$. The usual work-up gave crystals (25 mg) which were recrystallized from methanol to yield a specimen for analysis, mp 119—121°C. (Found: C, 80.50; H, 11.61%. Calcd for $C_{27}H_{46}O_2$: C, 80.55; H, 11.51%). IR 1735 (C=O), 1310, 1253, 1144, 1106, and 1024 $cm^{-1}$; $^1H$ NMR $\delta$= 0.65 (3H, s, 18-H), 0.95 (3H, s, 19-H), 2.44 (1H, br.d, $J$= 14.7 Hz, 7a-H), 2.97 (1H, m, 7a-H), and 4.17 (1H, br.s, 5$\beta$-H). MS *m/z* (rel intensity) 402 ($M^+$, 2%) and 318 (100).

**Preparation of *B*-Homo-6-oxa-5$\beta$-cholestan-7-one (18) by the Photo-Rearrangement.** 5-Hydroxy-5$\alpha$-cholestan-6-one[10] (240 mg) in ethanol (50 ml) in a Pyrex vessel was irradiated with a 450-W high pressure Hg arc (Eikosha-PIH 450) in an atmosphere of nitrogen for 50 h. The solvent was removed under reduced pressure and the residue was recrystallized from methanol to yield *B*-homo-6-oxa-5$\beta$-cholestan-7-one (174 mg). This lactone was identical with the lactone obtained by the oxidation of *B*-homo-6-oxa-5$\beta$-cholestane with ruthenium tetraoxide.

***B*-Homo-6-oxa-5$\beta$-cholestan-7$\alpha$- and 7$\beta$-ols (20).** A solution of DIBAL (0.25 ml) was added dropwise to a solution of lactone **18** (90 mg) in dry toluene (10 ml) at −78°C. The solution was stirred for 5 h at −78°C and poured into iced water. After the solution was filtered, the filtrate was washed with water and dried over anhydrous $Na_2SO_4$. The usual work-up gave an oily product. This was purified once by preparative TLC with a 10 : 1 benzene-diethyl ether to

yield a mixture of 7$\alpha$- and 7$\beta$-ols **20**. (Found: $m/z$ 404.3663. Calcd for $C_{27}H_{48}O_2$: M, 404.3655). IR 3260 (OH) and 1018 $cm^{-1}$ (C-O); $^1H$ NMR $\delta$= 0.65 and 0.66 (each 3H, each s, 18-H of 7$\alpha$- and 7$\beta$-ols), 2.61 and 2.75 (each 1H, each d, $J$= 3.9 Hz, OH of 7$\alpha$- and 7$\beta$-ols), 3.41 and 3.93 (each 1H, each t, $J$= 6.6 and 4.2 Hz, 5$\beta$-H of 7$\alpha$- and 7$\beta$-ols), 5.07 and 5.33 (each 1H, m, 7-H of 7$\alpha$- and 7$\beta$-H); MS $m/z$ (rel intensity) 404 ($M^+$, 2%), 386 [$(M-H_2O)^+$, 43], 249 (35), 140 (36), 112 (82), and 43 (100).

**Irradiation of the Hypoiodite of *B*-Homo-6-oxa-5$\beta$-cholestan-7-ols in ths Presence of Mercury(II) Oxide and Iodine.** Lactols **20** (24 mg) were dissolved in dry benzene (3 ml) containing pyridine (0.1 ml), mercury (II) oxide (26 mg) and iodine (31 mg). The solution in a Pyrex vessel was irradiated for 2 h in an atmosphere of nitrogen. After the removal of inorganic precipitates, the filtrate was worked up as usual to give an oily product (35 mg). This was subjected to preparative TLC with benzene to give two fractions. The less mobile fraction (10 mg) was lactone **18**. (Found: $m/z$ 530.2614. Calcd for $C_{27}H_{47}IO_2$: M, 530.2619). IR (neat) 1714 (CHO) and 1177 $cm^{-1}$ (OCHO); $^1H$ NMR $\delta$=0.69 (3H, s, 18-H), 1.02 (3H, s, 19-H), 3.33 (1H, dd, $J$= 10.74 and 2.92 Hz, $CH_2I$), 3.51 (1H, dd, $J$= 10.74 and 1.95 Hz, $CH_2I$), 4.87 (1H, br.s, 5$\beta$-H), and 8.23 (1H, s, CHO); MS $m/z$ (rel intensity) 530 ($M^+$, 0.2%), 403 ($M^+-I$, 0.7), 357 [$(M-I-OCH_2O)^+$, 48], 261 (18), 149 (36), 95 (96), and 83 (100).

**6-Oxa-5$\beta$-cholestane (22).** A solution of formate **21** (9 mg) in THF (3 ml) was cooled at −78°C. Methyllithium (0.57 M diethyl ether solution 0.08 ml) was added to this stirred solution. The solution was stirred for 2 h and the temperature of the solution was then raised to room temperature. The solution was then stirred for 1 h at room temperature and extracted with diethyl ether. The ethereal solution was worked up as usual to yield an oily product. This was purified by preparative TLC with benzene to yield a pure material (5.5 mg) (Found: $m/z$ 374.3564. Calcd for $C_{26}H_{46}O$: M, 374.3549). IR 1102 and 1086 $cm^{-1}$ (C-O); $^1H$ NMR $\delta$=0.67 (3H, s, 18-H), 1.07 (3H, s, 18-H), 3.34 (1H, dd, $J$= 12.2 and 4.40 Hz, 5$\beta$-H), 3.36 (1H, dd, $J$= 11.5 and 11.5 Hz, 7$\alpha$-H), and 3.53 (1H, dd, $J$= 11.5 and 5.4 Hz, 7$\beta$-H); MS $m/z$ (rel intensity) 374 ($M^+$, 36%), 219 (100), 201 (19), and 164 (16).

## References


1) Photoinduced Molecular Transformations. Part 91. Part 90. H. Suginome and S. Yamada, *Tetrahedron*, in press.

2) H. Suginome and S. Yamada, *J. Org. Chem.*, **49**, 3753 (1984).

3) H. Suginome and S. Yamada, *J. Org. Chem.*, **50**, 2489 (1985).

4) H. Suginome and S. Yamada, *Bull. Chem. Soc. Jpn.*, **58**, 3055 (1985).

5) H. Suginome and S. Yamada, *Synthesis*, **1986**, 741.

6) L. F. Fieser, T. Goto, and B. K. Bhattacharyya, *J. Am. Chem. Soc.*, **82**, 1700 (1960).

7) J. T. Edward and P. F. Morand, *Can. J. Chem.*, **38**, 1325 (1960).

8) N. J. Doorenbos and M. T. Wu, *J. Org. Chem.*, **26**, 4550 (1961).

9) B. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4557 (1961).

10) L. M. Berkowitz and P. N. Rylander, *J. Am. Chem. Soc.*, **80**, 6682 (1958); A. B. Smith, III and R. M. Searborough, Jr., *Synth. Commun.*, **10**, 205 (1980).

11) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 579 (1950).

12) H. Lettré and D. Hotz, *Liebigs Ann. Chem.*, **620**, 63 (1959).

13) H. Reich, F. E. Walker, and R. W. Collins, *J. Org. Chem.*, **16**, 1753 (1951); D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, **1955**, 2876; T. Suga, T. Shishibori, and T. Matsuura, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 171.

14) R. C. Cookson, R. P. Gandhi, and R. M. Southam, *J. Chem. Soc. C*, **1968**, 2494.

15) H. Suginome and S. Yamada, *Chem. Lett.*, **1984**, 2479.

16) For reviews, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco (1967), p. 205.

17) L. Tökés, G. Jones, and C. Djerassi, *J. Am. Chem. Soc.*, **90**, 5465 (1968).

18) D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, **1957**, 935; For reviews, see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publ., New York (1965) p. 345; R. Bucourt, in "Topics in Stereochemistry," ed by, E. L. Eliel and N. L. Allinger, Wiley, New York (1974), Vol. 8, p. 159.

19) H. Budzikiewicz, J. Buchler, and G. Quinkert. The work cited in Ref. 16.

20) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 2920 (1965).