Regioselective β-Scission of α-Oxoalkoxyl Radicals: a Novel Formation of α-Hydroxy ε-Lactones by Photolysis of Steroidal α-Oxo Alcohol Hypoiodites in the Presence of Mercury(II) Oxide and Iodine[1]

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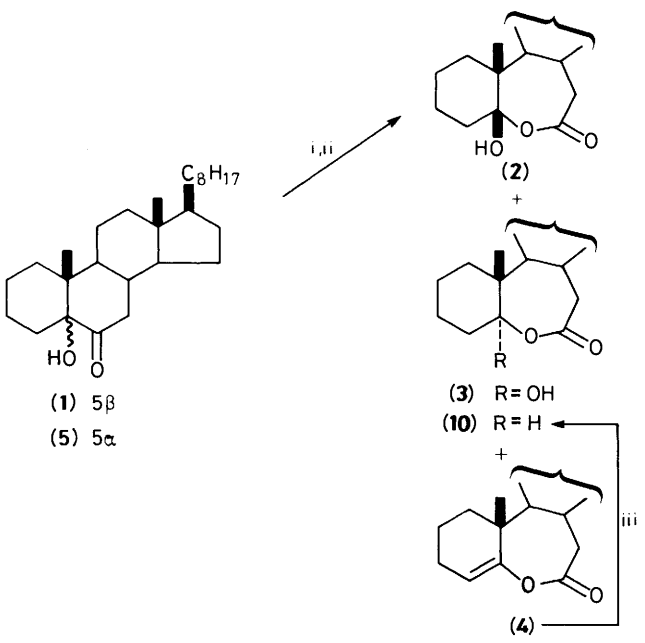
Irradiation of hypoiodites of steroidal α-oxo tertiary alcohols in the presence of mercury(II) oxide and iodine in benzene gave α-hydroxy ε-lactones and enolic ε-lactone; the mechanism of their formation is discussed on the basis of an ^{18}O labelling study.

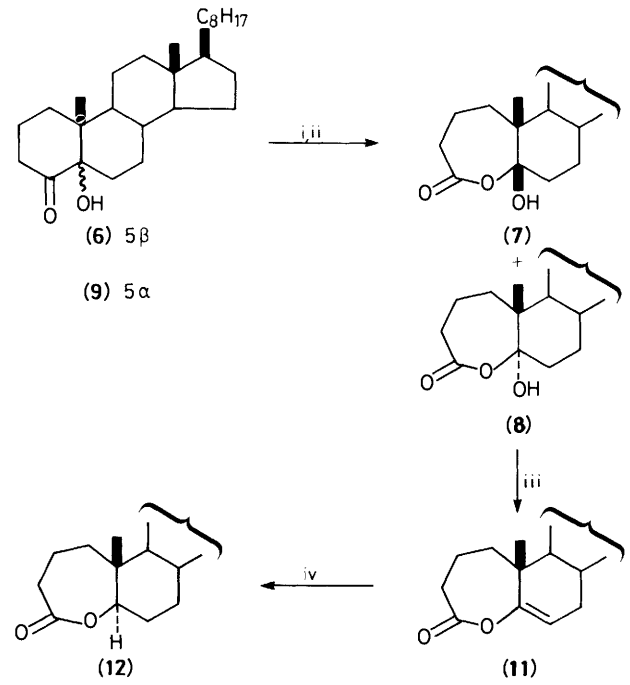
In a continuation of our exploration of the potential utility of the β-scission of alkoxyl radicals in organic synthesis,[2] we have investigated the behaviour of steroidal alkoxyl radicals carrying an α-oxo group. We now report that the irradiation of the hypoiodites of steroidal α-oxo tertiary alcohols such as 5β- and 5α-hydroxycholestan-6-one [(**1**) and (**5**) respectively] and 5β- and 5α-hydroxycholestan-4-one [(**6**) and (**9**) respectively] resulted in a novel formation of α-hydroxy lactones; this arose from regioselective scission of the bond between the carbonyl and the carbon carrying an alkoxyl radical.

Thus irradiation of the hypoiodites, prepared *in situ* through the reaction of 5β-hydroxycholestan-6-one (**1**)[3] with 3 equiv. of mercury(II) oxide and iodine in benzene, gave a product mixture from which a 1:1 mixture of the hydroxy lactones (**2**) and (**3**) (25% yield) and a crystalline lactone (**4**) (18%) were isolated by preparative t.l.c. Similarly, irradiation of the hypoiodite of the 5α-epimer (**5**)[3] produced a mixture of the epimers (**2**) and (**3**) (14%) and the enol lactone (**4**) (10%). The structure of the lactone (molecular formula $C_{27}H_{44}O_2$ by high resolution mass spectrometry) was established as 6-oxa-B-homocholest-4-en-7-one (**4**) by i.r., ^1H n.m.r., and mass spectroscopy† and by its

† $\nu_{max.}$(neat) 2 936 (OH), 1 748 (lactone C=O), and 1 673 cm^{-1} (enolic C=O); δ(270 MHz) 0.69 (3 H, s, 18-H), 0.88 (3 H, s, 19-H), and 5.40 (1 H, dd, *J* 4.0 and 3.6 Hz, 4-H); *m/z* 400 (M^+, 37.7) and 372 [$(M - CO)^+$, 100%].



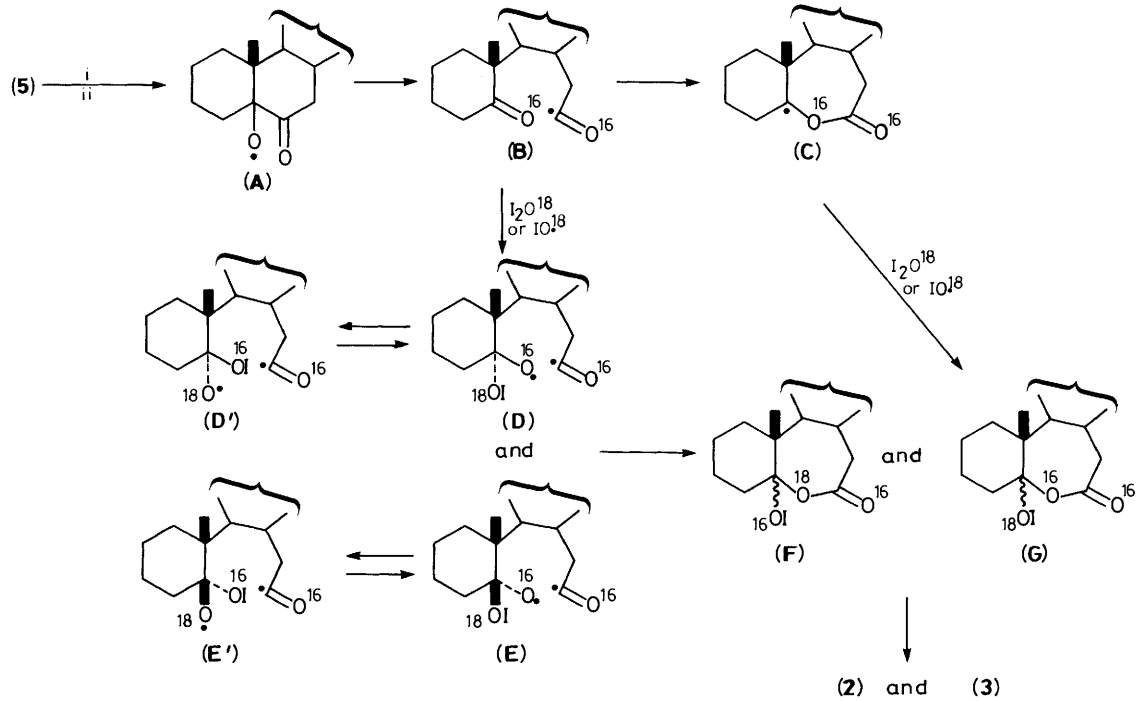
Scheme 1. *Reagents and conditions:* i, HgO, I_2, C_6H_6; ii, *hv*; iii, PtO_2, H_2, AcOH



Scheme 2. *Reagents and conditions:* i, HgO, I_2, C_6H_6; ii, *hv*; iii, AcCl–Ac_2O; iv, PtO_2, H_2, AcOH

catalytic hydrogenation (PtO_2–AcOH) to 6-oxa-B-homo-5α-cholestan-7-one (**10**).[4] The inseparable mixture of epimeric hydroxy lactones (**2**) and (**3**) was characterized by its i.r., ^1H n.m.r., and mass spectra* as a mixture of 5-hydroxy-6-oxa-B-homo-5β- and 5α-cholestan-7-one, respectively. Dehydration of the mixture with acetyl chloride–acetic anhydride under reflux for 24 h gave the enolic lactone (**4**) in 60% yield. The ratio of the epimers was estimated to be 1:1 on the basis of the integrals of the 19-H signals.

5β-Hydroxycholestan-4-one (**6**)[5] and its 5α-epimer (**9**)[5] were then subjected to the same conditions as those imposed on the 5-hydroxycholestan-6-ones. The photolysis gave a 1:1 mixture† of 5-hydroxy-4a-oxa-A-homo-5β- and 5α-cholestan-4-ones (**7**)



Scheme 3. *Reagents and conditions:* i, $Hg^{18}O$, I_2; ii, *hv*

* $\nu_{max.}$(neat) 3 400 (OH) and 1 704 cm^{-1} (lactone C=O); δ(270 MHz) 1.01 [3 H, s, 19-H of lactone (**3**)] and 1.26 [3 H, s, 19-H of lactone (**2**)].

† $\nu_{max.}$(neat) 3 425 (OH) and 1 702 (lactone C=O); δ(270 MHz) 1.07 [3 H, s, 19-H of (**8**)], 1.26 [3 H, s, 19-H of (**7**)], and 0.72 (6 H, s, 18-H); *m/z* 418 (M^+, 0.34) and 332 (100%).

Table. Mass spectrometric determination of ^{18}O incorporation from $Hg^{18}O$–I_2 treatment of (**1**), (**5**), (**6**), and (**9**)

Product	*m/z*	(M^+)	Intensity (%)	Calc'd incorporation of $Hg^{18}O$ oxygen (%)
(**2**) and (**3**)	418	^{16}O	0.20	47
	420	^{18}O	0.14	
(**11**)	400	^{16}O	10.47	16
	402	^{18}O	1.76	
(7) and (**8**)	418	^{16}O	0.24	38
	420	^{18}O	0.12	
(**4**)	400	^{16}O	7.19	11
	402	^{18}O	0.77	
(**4**)*	400	^{16}O	15.44	19
	402	^{18}O	3.16	

* Prepared by dehydration of hydroxy lactones (**2**) and (**3**).

and (**8**) in 42% yield, but with no accompanying formation of an enol lactone such as (**4**) (Scheme 2). The structures were confirmed by spectroscopy and by transformation into the known 4a-oxa-A-homo-5α-cholestan-4-one (**12**).[6] Thus dehydration of the hydroxy lactones (**7**) and (**8**) with acetic anhydride and acetyl chloride afforded 4a-oxa-A-homocholest-5-en-4-one (**11**)* in 10% yield. Catalytic hydrogenation of the enolic lactone (**11**) gave 4a-oxa-A-homo-5α-cholestan-4-one (**12**)[6] in 90% yield.

It should be noted that no product derived from β-scission of the C(5)–C(10) bond of the α-hydroxy ketones[7] or lactols[8] were formed in the present reaction, as proved by the absence of any signals due to olefinic products[7] in the ^1H n.m.r. spectra of the crude products.

The regioselective introduction of the extra oxygen into the products of the present reaction raised our interest about the origin of the oxygen; we established this by means of an ^{18}O labelling experiment.[9] The results of the mass spectrometric determination of the incorporation of ^{18}O into the products (**2**), (**3**), (**4**), (**7**), (**8**), and (**11**), obtained from the reactions induced by mercury(II) oxide labelled with ^{18}O,† are shown in the Table. These results indicate that an oxygen atom of mercury(II) oxide is incorporated in either the hydroxy group or the ring oxygen of the hydroxy ε-lactones (**2**), (**3**), (**7**), and (**8**) and partially incorporated in the ring oxygen of the enolic ε-lactone (**4**).

The proposed mechanism for formation of the ε-lactones to account for the labelling results is summarized in Scheme 3. Regioselective β-scission of the alkoxyl radical (**A**) gives an intermediate radical (**B**). The observed incorporation of ^{18}O as the ring oxygen in all the products can be understood by postulating the addition of iodoxyl radical to the carbonyl carbon of the radical (**B**) to give the hypoiodites (**D**) and (**E**), followed by cyclization to the hydroxy ε-lactones such as (**2**) and (**3**). Another possible route leads from the radical (**B**) to give rise to an hydroxy ε-lactone in which ^{18}O is incorporated only in the hydroxy group. An intramolecular combination of the carbonyl oxygen and the C-6 terminus of the radical (**B**) thus gives lactone radical (**C**). The combination of the species (**C**) and iodoxyl radical may give the α-hydroxy ε-lactone (**G**).

* $\nu_{max.}$(Nujol) 2 868 (OH), 1 750 (lactone C=O), and 1 688 cm^{-1} (C=C); δ(270 MHz) 0.69 (3 H, s, 18-H), 1.07 (3 H, s, 19-H), and 5.40 (1 H, dd, *J* 2.0 and 5.3 Hz, 6-H); *m/z* 400 (M^+, 13.2) and 372 (100%).

† Mercury(II) [^{18}O]oxide (88 atom% ^{18}O) was prepared as before.[9]

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