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A New Sequential Alkoxy Radical Fragmentation of δ-Hydroxyketones

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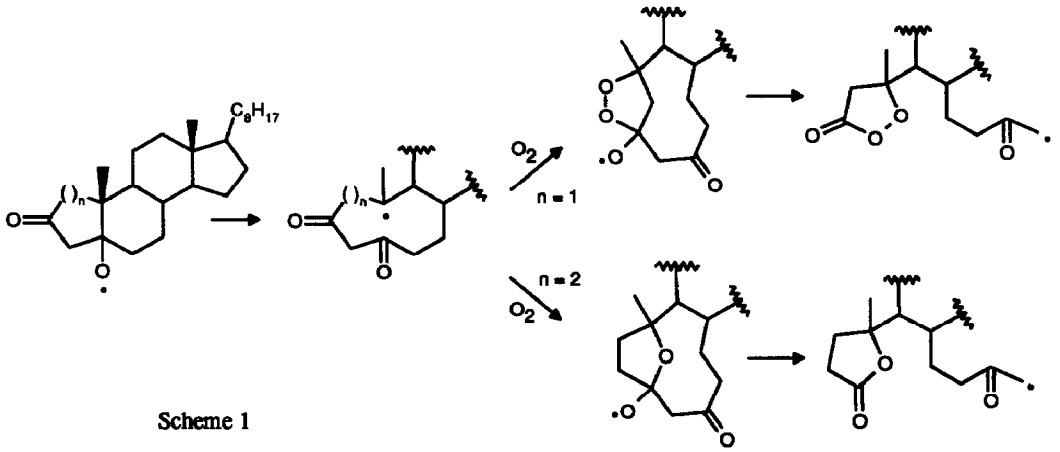
Abstract: *The alkoxy radicals formed by the reaction of steroidal cyclic hydroxyketones (1) and (2) with (diacetoxyiodo)benzene and iodine or mercuric oxide and iodine under oxygen atmosphere and irradiation with visible light undergo a new quintuple sequence β-fragmentation-peroxidation-radical reduction-radical cyclization-β-fragmentation reaction before being trapped by an atom of iodine.*

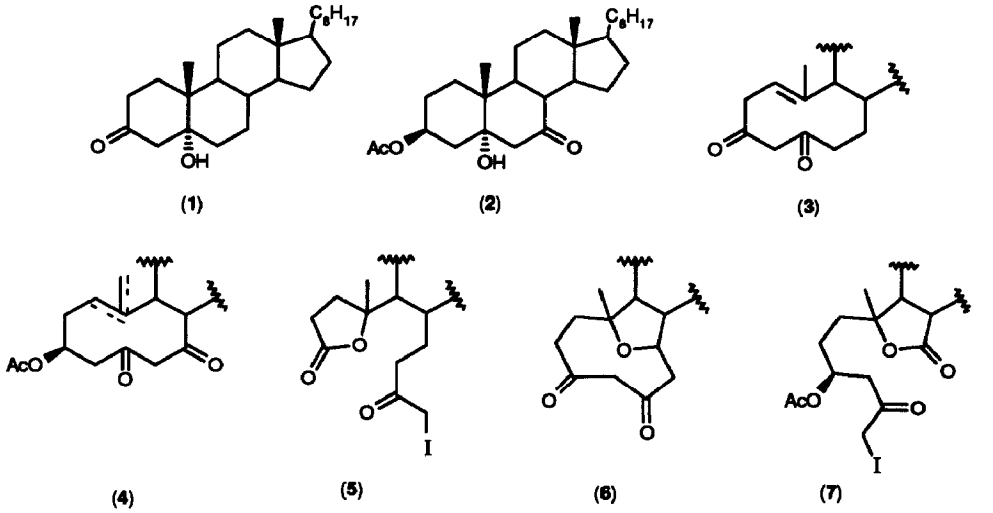
In the past few years, together with the resurgence in carbon-centered radical chemistry a concurrent interest in alkoxy radicals has occurred.[1] We have recently reported that the β-fragmentation reaction of alkoxy radicals, generated by treatment of tertiary alcohols with (diacetoxyiodo)benzene and iodine under irradiation with visible light, leads in the presence of oxygen to peroxidation of the initially produced C-radical by trapping molecular oxygen.[2] The resultant peroxy radical is able to react with a suitably positioned carbonyl group yielding β-peroxylactones (n=1, Scheme 1).[3]

When we applied this methodology to steroidal hydroxyketones where n=2 (Scheme 1) we obtained γ-lactones instead of the expected γ-peroxylactones. In this communication we describe our preliminary results on this reaction and a plausible mechanism for it.



Scheme 1

Steroidal tertiary alcohols (**1**)[4] and (**2**)[5] were used as models. These compounds were treated with (diacetoxyiodo)benzene (DIB) and iodine or mercuric oxide and iodine under irradiation with two 100 W tungsten-filament lamps under the conditions summarized in the Table. When the reaction was performed under argon (entries 1 and 6) the C-radicals formed by β-fragmentation of alkoxy radicals eliminated to



produce olefins (**3**)[6] and (**4**) respectively. When the photolysis was conducted under oxygen (entries 2-5 and 7-9) γ-lactones (**5**)[7] and (**7**)[8] were obtained. In the case of compound (**1**), the tetrahydrofuran (**6**)[9] was also produced. The photolysis was conducted under different oxygen pressures, the best yields of oxygenated products being obtained with air (entries 2, 7 and 8) or low oxygen pressures (entries 3, 4 and 9). Increasing oxygen pressure does not improve the yield (entry 5).

A plausible mechanism for the generation of these products, applied to the photolysis of model (**1**), is shown in Scheme 2. As can be seen, the sequence is initiated by the C-5 alkoxy radical that undergoes C_5-C_{10} fragmentation and the resulting C-10 radical can be stabilized by elimination to give olefin (**3**) or react with molecular oxygen generating peroxy radical (I), which is reduced in the reaction mixture to alkoxy radical (II). The latter may add to the carbonyl group [path a] producing a new alkoxy radical that can undergo β-fragmentation affording a C-radical at C-4. This intermediate can trap an iodine atom yielding γ-lactone (**5**). Alternatively [path b], radical (II) may abstract a hydrogen atom at C-7 and cyclize to give the tetrahydrofuran (**6**). A similar process has been reported previously for the generation of other cyclic ethers.[2a,3a]

Because of the relative weakness of the peroxide bond the catalyzed homolysis of the peroxy radical to the alkoxy radical is a very easy process and, due to its biological importance, a well-documented one.[10] In our case this homolytic reaction may be catalyzed by radical species or traces of metal ions in the medium.[11] Alternatively, we thought of iodobenzene formed from DIB as the reducing agent. Unfortunately, addition of the former to the reaction mixture (entry 4) did not improve the yields of the oxygenated products.

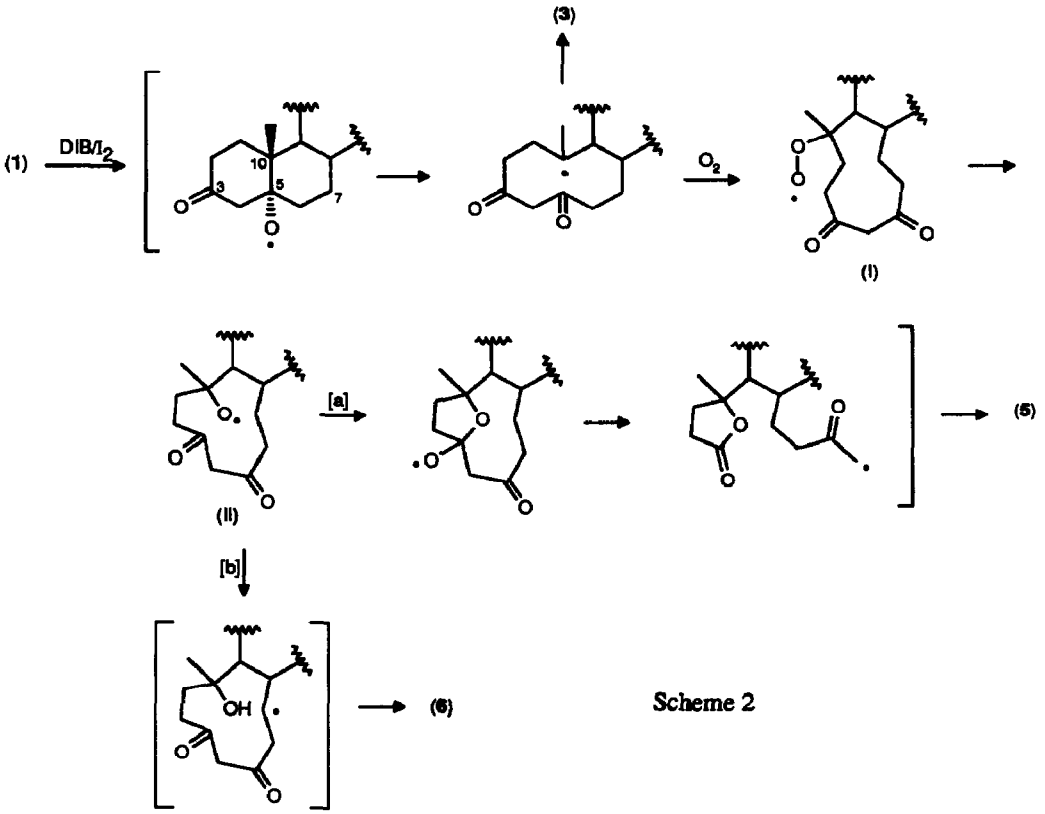
When the peroxy radical was added directly to the carbonyl group (Scheme 1, n = 1) β-peroxylactones were formed in more than 40% yield.[3b] Nevertheless, the addition of the alkoxy radical gave a relatively low yield of γ-lactones (10%) (Scheme 1, n = 2). However, taking into account that seven steps are involved in this sequence, each of them must have a yield of about 70% to account for the final result. It is noteworthy that no formation of γ-peroxylactones was observed either from (**1**) or (**2**), probably because in radical cyclizations the formation of a five-membered ring is normally preferred to that of a six-membered ring.

This is an interesting and unprecedented example of a 5-step radical reaction, β-fragmentation-peroxidation-radical reduction-radical cyclization-β-fragmentation, undergone by an initially formed alkoxy radical.

Table. Sequential alkoxy radical fragmentation[a]

Entry	Substrate	Reagents[b] (mmol)	Solvent	Conditions			Products (yield %)
				T. (°C)	P. (atm)	Time (h)	
1	**1**	DIB/I_2 (3, 1.5)	Cy	40	Ar (1)	1	**3** (16)
2	**1**	DIB/I_2 (2.5, 2)	Cy	40	air (1)	0.75	**5** (3), **6** (2)
3	**1**	DIB/I_2 (2,1)	Cy	40	O_2 (3)	0.5	**3** (14), **5** (8), **6** (19)
4	**1**	DIB/I_2/PhI (2,1,2)	Cy	40	O_2 (3)	0.5	**3** (10), **5** (10), **6** (13)
5	**1**	DIB/I_2 (2.5,1.5)	Cy	r.t.	O_2 (10)	3	**3** (4), **5** (7), **6** (19)
6	**2**	DIB/I_2 (1.5,1)	Cy	40	Ar (1)	6	**4** (12)
7	**2**	DIB/I_2 (1.5,1)	Cy	40	air (1)	5	**7** (10)
8	**2**	HgO/I_2 (5,3)	CCl_4	45	air (1)	3	**7** (9)
9	**2**	HgO/I_2 (5,3)	CCl_4	45	O_2 (3)	1.5	**7** (12)

[a] All reactions were performed by irradiation with two 100 W tungsten-filament lamps; those under pressure were performed in a borosilicate Griffin-Worden pressure vessel (Kontes K-767100). [b] per mmol of substrate. DIB = (diacetoxyiodo)benzene; Cy = cyclohexane.



Scheme 2

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4. Compound (1): m.p. 211-213 °C (acetone), $[\alpha]_D$ +40.6° ($CHCl_3$, c, 0.32); IR ($CHCl_3$) ν_{max} 3540, 1700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.68 (3H, s, 13-Me), 0.86 (6H, d, *J* 6.6 Hz, 25-Me_2), 0.90 (3H, d, *J* 8.5 Hz, 20-Me), 1.17 (3H, s, 10-Me), 2.11 (1H, d, *J* 15.1 Hz, 4-H_a), 2.86 (1H, d, *J* 15.1 Hz, 4-H_b); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 211.27 (s, C-3), 77.68 (s, C-5); MS m/z 402.3500 (M^+, 15%).
5. Compound (2): m.p. 220-222 °C (acetone-hexane), $[\alpha]_D$ -41° ($CHCl_3$, c, 0.196); IR ($CHCl_3$) ν_{max} 3594, 1716 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.65 (3H, s, 13-Me), 0.86 (6H, d, *J* 6.4 Hz, 25-Me_2), 0.91 (3H, d, *J* 6.4 Hz, 20-Me), 1.25 (3H, s, 10-Me), 2.02 (3H, s, OAc), 2.04 (1H, d, *J* 13.1 Hz, 6-H_a), 2.78 (1H, d, *J* 13.1 Hz, 6-H_b), 5.11 (1H, m, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 210.34 (s, C-7), 170.84 (s, CO), 79.10 (s, C-5), 70.49 (d, C-3); MS m/z 460.35445 (M^+, 1%).
6. Compound (3): m.p. 130.6-132.5 °C (*n*-hexane), $[\alpha]_D$ +327.7° ($CHCl_3$, c, 0.36); IR ($CHCl_3$) ν_{max} 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.71 (3H, s, 13-Me), 0.86 (6H, d, *J* 7.4 Hz, 25-Me_2), 0.90 (3H, d, *J* 7.0 Hz, 20-Me), 1.73 (3H, s, 10-Me), 2.68 (1H, dd, *J* 14.8, 6 Hz, 2-H), 2.84 (1H, d, *J* 16 Hz, 4-H_a), 4.32 (1H, d, *J* 16 Hz, 4-H_b), 3.49 (1H, dd, *J* 11, 14.8 Hz, 2-H), 5.23 (1H, m, 1-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 208.94 (s, C-5), 203.77 (s, C-3), 144.62 (s, C-10), 118.63 (d, C-1); MS m/z 400.33364 (M^+, 36%).
7. Compound (5): Amorphous; IR ($CHCl_3$) $\nu_{max.}$ 1760, 1708 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.70 (3H, s, 13-Me), 0.86 (6H, d, *J* 6.4 Hz, 25-Me_2), 0.91 (3H, d, *J* 7.1 Hz, 20-Me), 1.39 (3H, s, 10-Me), 3.83 (1H, d, *J* 10 Hz, 4-H_a), 3.93 (1H, d, *J* 10 Hz, 4-H_b); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 203.64 (s, C-5), 176.12 (s, C-3), 90.12 (s, C-10), 6.64 (t, C-4); MS m/z 542.23683 (M^+, 6%).
8. Compound (7): Amorphous; IR ($CHCl_3$) ν_{max} 1762, 1736 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.68 (3H, s, 13-Me), 0.87 (6H, d, *J* 6.6 Hz, 25-Me_2), 0.93 (3H, d, *J* 6.4 Hz, 20-Me), 1.39 (3H, s, 10-Me), 2.05 (3H, s, OAc), 2.99 (2H, d, *J* 6.2 Hz, 4-H_2), 3.81 (H, d, *J* 10 Hz, 6-H_a), 3.84 (H, d, *J* 10 Hz, 6-H_b), 5.23 (1H, m, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 199.76 (s, C-5), 176.77 (s, C-7), 170.47 (s, OAc), 86.41 (s, C-10), 70.12 (d, C-3), 6.09 (t, C-6); MS m/z 542.22722 (M^+-AcOH, 1%).
9. Compound (6): m.p. 64-66 °C (methanol), $[\alpha]_D$ +90° ($CHCl_3$, c, 0.07); IR ($CHCl_3$) ν_{max} 1713, 1686 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 0.72 (3H, s, 13-Me), 0.87 (6H, d, *J* 6.6 Hz, 25-Me_2), 0.93 (3H, d, *J* 6.4 Hz, 20-Me), 1.26 (3H, s, 10-Me), 2.32 (1H, dd, *J* 12.2, 2.8 Hz, 6-H_a), 3.22 (1H, dd, *J* 12.2, 5.4 Hz, 6-H_b), 3.54 (2H, s, H-4), 3.87 (1H, m, H-7); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C *inter alia* 82.25 (s, C-10), 78.18 (d, C-7); MS m/z 416 (M^+, 22%).
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