Carbonyl Compounds by Osmium Tetroxide Oxidation: Preferential Oxidation of Primary over Secondary Hydroxy Groups

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Osmium tetroxide has been widely used for hydroxylation of olefins, but has received little attention in the oxidation of alcohols[1]. The kinetics of osmium tetroxide-catalysed oxidation of primary and secondary hydroxy groups by different co-oxidants in alkaline medium have been studied[2]. Ruthenium tetroxide is a highly effective oxidant for the conversion of secondary alcohols into ketones and primary alcohols into aldehydes and carboxylic acids, but it lacks selectivity[3].

We have consequently undertaken a study on the oxidation of alcohols with osmium tetroxide, in spite of its toxicity, to see if this reagent shows a behaviour different from that of ruthenium tetroxide.

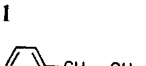
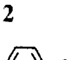
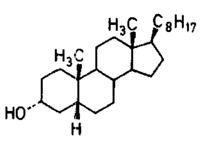
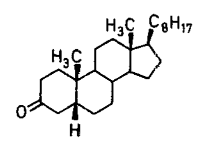
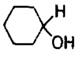
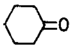
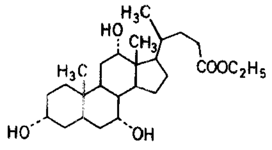
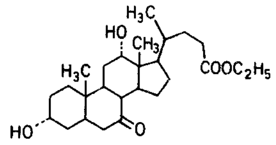
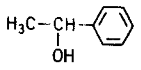
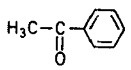
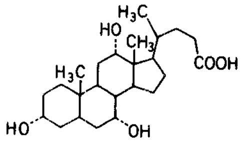
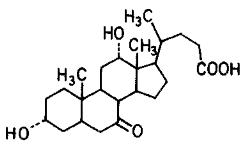
Results obtained in the oxidation of 3β-cholestanol (**1**) by means of osmium tetroxide in comparison with ruthenium tetroxide are reported as a first example in this communication. The reaction was always performed in diethyl ether, under mild conditions, and can be carried out in different

Table 1. Oxidation of 3β-cholestanol (**1**) with Osmium Tetroxide in Comparison with Ruthenium Tetroxide

Oxidant	Environmental/ Conditions	Molar Ratio Alcohol/ Oxidant	Yield[a] [%] of **2**
osmium tetroxide	neutral	1/1	50
ruthenium tetroxide	neutral	1/1	49[3]
osmium tetroxide	acidic	1/1	80
ruthenium tetroxide	acidic	1/0.1	19[3]
osmium tetroxide	acidic	1/0.1	30
ruthenium tetroxide	neutral	1/0.1	30[3]

[a] Yield of pure isolated product.

Table 2. Acid-Catalysed Oxidation of Alcohols with Osmium Tetroxide

Alcohol	Product	Yield [%][a]
1	**2**	80[b]
		92[c]
		90[b]
		75[c]
		70[b,d]
n-$C_{12}H_{25}$–OH	n-$C_{11}H_{23}$–CH=O	70[c]
		70[c]
		25[b,d,e,f]

[a] Yield of pure isolated product.

[b] Yields determined by column chromatography (silica gel, benzene as eluent). The keto compounds were compared with authentic samples.

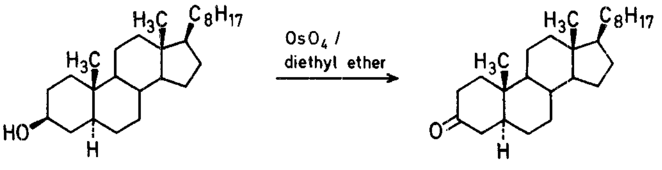
[c] Yields determined by G.L.C. C20M PEG 3%, 5m, 130°C.

[d] A 1/3 molar ratio alcohol/oxidant was used.

[e] Diethyl ether/pyridine 1/1 was used as solvent without acid catalysis.

[f] Yields determined by T.L.C. on silica gel plates 0.5 mm thick (cyclohexane/ethyl acetate/acetic acid 9/24/0.5 as eluent). Starting material 50% was recovered.

ways: (A) homogeneous neutral environment, (B) non-aqueous homogeneous acidic medium (the reaction undergoes acid catalysis. The yields of oxidation product reach a maximum at an equimolar ratio alcohol/acid and then decrease for higher acid concentrations[4]), (C) heterogeneous acidic medium using catalytic amounts of osmium tetroxide. In spite of the difficulties in separating the keto-derivative **2** from precipitated osmium oxide, good yields of cholestanone have been obtained without overoxidation products being formed (Table 1).

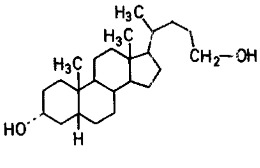
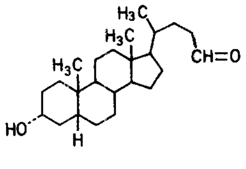
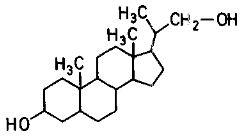
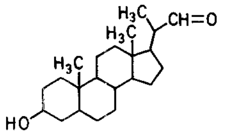
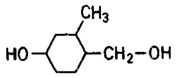
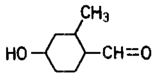
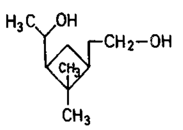
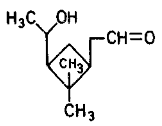


1 **2**

It is well known that an axial hydroxy group can be more easily oxidized with usual reagents than the corresponding equatorial one. This was further confirmed when the 3α-cholestanol or ethyl cholate have been treated with osmium tetroxide. In the first case, cholestanone has been obtained in 90 % yield while for the latter product only the 7-keto derivative (position 7 is more reactive) was isolated in a 30 % yield at room temperature and in 70 % yield at 40 °C. Results are summarized in Table 2, where the behaviour of osmium tetroxide with other alcohols has also been reported.

It can be observed that osmium tetroxide is a highly effective oxidant for the conversion of secondary alcohols into ketones and of primary alcohols into aldehydes under homogeneous, mild conditions. The oxidation by osmium tetroxide shows the same mechanism of the common hydride transfer acid-catalysed reaction (well known for ruthenium tetroxide and transition metal complexes), that involves a pair of successive two electron transfer steps[5]. From the results reported above, it is possible to observe that osmium tetroxide leads only to aldehydic derivatives in the oxidation of primary hydroxy groups, while ruthenium tetroxide gives also carboxylic compounds[3].

Table 3. Selective Oxidation at Primary Carbon Atoms by Osmium Tetroxide

Primary-secondary diol	Hydroxyaldehyde	Yield [%][a]
3 	**4** 	50[b]
5 	**6** 	40[b]
7 	**8** 	30[c]
9 	**10** 	30[c]

[a] Yield of pure isolated product.

[b] Yields determined by column chromatography on silica gel (benzene/ethyl acetate 8/2 as eluent). The I.R. and ^{1}H-N.M.R. spectra were in good agreement with those of authentic samples. Starting material was recovered.

[c] The compounds were isolated by T.L.C. on silica gel plates 0.5 mm thick (benzene/ethyl acetate 9/1 as eluent).

Table 4. Physical and Spectral Data for Compounds **3–10** (Table 3)

Compound	m.p. [°C]	Molecular Formula[a] or Lit. m.p. [°C]	[α]$_D$ found	[α]$_D$ reported	I.R. (CHCl$_3$) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm][b]
3	170–171°	170–172°[7]	+37°	+35°[7]	–	–
4	145–147°	146–149°[8]	+29	+28°[8]	3600 (br.); 2710, 1720	0.64 (s, 3H, 13-CH$_3$); 0.94 (s, 3H, 10-CH$_3$); 4.05 (m, 1H, 3β-H); 9.80 (d, 1H, $J = 2$ Hz, —CH=O)
5	231–232°	231–232°[9]	+26°	+26°[9]	–	–
6	157–159°	158–160°[9]	+11°	+11°[9]	3400 (br); 2710, 1725	0.70 (s, 3H, 13-CH$_3$); 0.80 (s, 3H, 10-CH$_3$); 1.00 (d, 3H, $J = 6$ Hz, 20-CH$_3$); 3.60 (m, 1H, 3α-H); 9.60 (d, 1H, $J = 3.5$ Hz, —CH=O)
7	oil[c]	$C_8H_{16}O_2$ (144.2)	–	–	3500 (br)	–
8	oil	$C_8H_{14}O_2$ (142.2)	–	–	3500 (br); 2715, 1720	0.6 (m, 1H); 0.75 (m, 1H); 1.15 (s, 3H); 1.45 (m, 1H); 2.6–3.3 (m, 4H); 3.85 (m, 1H); 9.55 (s, 1H, —CH=O)
9	oil[d]	$C_{10}H_{20}O_2$ (172.2)	–	–	3600 (br)	–
10	oil	$C_{10}H_{18}O_2$ (170.2)	–	–	3600 (br); 2710, 1725	0.85 (s, 3H); 1.1 (s, 3H); 1.3 (s, 3H) 3.4–3.8 (m, 3H); 9.74 (s, 1H —CH=O)

[a] Satisfactory microanalyses obtained: C ±0.20, H ±0.10.

[b] Recorded on a Varian EM390 spectrometer.

[c] This diol was obtained from 4-ethoxycarbonyl-3-methyl-2-cyclohexen-1-one by catalytic hydrogenation and subsequent lithium aluminium hydride reduction of saturated product.

[d] This diol was obtained from (±)-methyl *cis*-pinonate as described in Ref.[10].

Furthermore we have examined if osmium tetroxide may present a different reactivity towards the primary and secondary hydroxy groups in the primary and secondary diols reported in Table 3. It is worth noting that treatment of these diols with osmium tetroxide always gives hydroxyaldehydes arising from a selective oxidation at the primary carbon atom. These results represent an interesting approach to the problem of selective oxidation of alcohols since only a few efficient methods for the preferential oxidation of primary over secondary hydroxy groups can be found in literature[6].

Oxidation of 3β-Cholestanol (1) by Osmium Tetroxide:

The solvent was found to be critical (use of anisole, diethyl ether, *t*-butanol, or tetrahydrofuran led to satisfactory yields of oxidation product, but in dichloromethane, ethyl acetate, dimethyl sulfoxide, or dioxan, little or no reaction occurred). Therefore, all reactions described below were performed in diethyl ether.

Method A, *non-aqueous, homogeneous, neutral environment:* To a solution of 3β-cholestanol (**1**; 0.5 mmol) in diethyl ether (5 ml) is added an ether solution (5 ml) containing osmium tetroxide (0.5 mmol) and the mixture is stirred for 30 h at room temperature. Then an aqueous solution of sodium metabisulphite (0.5 mmol) is added and stirring is continued for 1 h. The oxidation product **2** is separated from precipitated osmium oxide by filtration on celite and the ethereal dilute solution is washed until neutrality and chromatographed on silica gel (benzene as eluent). The first fractions give cholestanone, which is compared with an authentic sample.

Method B, *non-aqueous, homogeneous, acidic environment:* The reaction is carried as described above, but with the addition of an equimolar quantity glacial acetic acid and then is worked-up as described above.

Method C, *heterogeneous, acidic medium with a catalytic amount of osmium tetroxide:* To 3β-cholestanol (**1**; 0.5 mmol) in diethyl ether (5 ml) is added osmium tetroxide (0.05 mmol), glacial acetic acid (0.5 mmol), and sodium chlorate (1.5 mmol) in water (1 ml). Work-up as described above gives cholestanone; yield: 30%. Starting material (50%) is also recovered.

Method D, *larger-scale (10 mmol) procedure:* To 3β-cholestanol (**1**; 3.9 g, 10 mmol) in diethyl ether (100 ml) is added an ethereal solution containing osmium tetroxide (2.5 g, 10 mmol) and glacial acetic acid (10 mmol).The mixture is stirred for 30 h at room temperature. After addition of sodium metabisulphite (10 mmol), work-up as described above gives a residue (3.7 g), which is crystallized from acetone; yield: 3.0 g (78%); m.p. 128–129 °C (Ref.[3].; m.p. 129–130 °C).

Acid-Catalysed Oxidation of Alcohols by Osmium Tetroxide; General Procedure:

One mmol of osmium tetroxide is employed for each hydroxy group and the experimental conditions are as described for Methods A and B above.

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