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CATALYTIC OXYGENATION OF β,γ-UNSATURATED 3-KETOSTEROIDS IN THE PRESENCE OF RUTHENIUM TETRAMESITYLPORPHYRIN COMPLEXES

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Cholest-5-ene-3-one **1** is oxidized by air at room temperature in the presence of trans-dioxoruthenium(VI)tetramesitylporphyrin $Ru(O)_2$ (tmp) to a mixture of the 6β- and 6α-alcohols **3** and **4**, and of the enedione **5**. Similar results are obtained in the presence of carbonylruthenium(II)tetramesitylporphyrin Ru(CO) (tmp) as catalyst. Iron(III) and manganese(III) tetramesitylporphyrins are weakly active or inactive as catalysts for the aerobic oxidation of **1**. Similarly, 17β-acetoxy-estr-5(10)-ene-3-one **2** is oxidized to 17β-acetoxy-10β-hydroxyestr-4-ene-3-one **7** in 42% yield in a highly β-stereoselective manner in the presence of $Ru(O)_2$ (tmp).

Keywords: Partial oxidation, steroids, porphyrins; ruthenium catalysts; ketone formation.

1. Introduction

Previous investigations in these laboratories have been focussed on the synthetic applications of the Groves-Quinn catalytic system [1] in the field of steroid chemistry: the solutions obtained by m-chloroperbenzoic (mCPBA) oxidation of carbonylruthenium(II) tetramesitylporphyrin Ru(CO) (tmp) have been shown to catalyze the aerobic epoxidation of various Δ^5 steroids such as cholesteryl esters, androstenone acetate, pregnenolone acetate, and cholest-5-ene-3-one ethylen-eketal [2–4]. Despite its slow kinetics [5], this catalytic system exhibits unique features which make it well suited as epoxidizing agent for this class of substrates: it uses an inexpensive oxygen source (air), it affords a clean conversion of the Δ^5 steroid to its epoxide in high yield, and it shows a high degree of β-stereoselectivity (> 98%) [3,4].

On the other hand, dehydrocholesterol and ergosterol esters as substrates of the Groves-Quinn catalyst have been found to exhibit a completely different

behaviour: their conjugated 5,7-diene system is attacked regiospecifically at the 5,6 double bond in a very fast, non-stereoselective reaction, and a mixture of the two epimeric 5,6α and 5,6β epoxides in a ca. 1 : 1 ratio is obtained in fair yield [4]. While the nearly complete β-stereospecificity for Δ^5 steroid epoxidation appears to be related to the steric bulk of the ortho-substituted phenyl groups of $Ru(O)_2$ (tmp) [6], the lack of stereoselectivity in the case of 5,7-diene systems has yet to be explained.

It was of interest to extend our investigations of this catalytic system to other types of steroid substrates, in order to assess further its potentialities as selective oxidation catalyst. In this paper, we report on the oxygenation of two β,γ-unsaturated 3-ketosteroids, **1** and **2**, catalyzed by ruthenium tetramesitylporphyrin complexes. The thermally [7]- and photochemically [8,9]-induced, as well as the platinum-catalyzed [10] oxygenations of cholest-5-ene-3-one **1** have been the topic of several earlier studies, while the epoxidation of the estr-5(10)-ene-3-one derivative **2** is of interest in the context of RU486 synthesis [11–13].

2. Results and discussion

Cholest-5-ene-3-one **1** in benzene solution was stirred in the presence of a catalytic amount of the dark brown complex $Ru(O)_2$ (tmp) [14]. In an early set of experiments, the progress of the reaction was monitored by tlc on silica. Several oxidation products appeared immediately, and no starting material could be detected after 5 minutes. However, we later found that a dramatic enhancement of the ruthenium-porphyrin-catalyzed oxidation rate of **1** is obtained in the presence of silica gel. Therefore, analytical data obtained by tlc do not reflect the actual product distribution in the reaction vessel in this case. Thus, the course of the catalytic oxidation was consistently monitored by ^1H nmr in the following sets of experiments. The reaction reached near completion after about two days, and the three products were separated by preparative tlc on silica gel. Compounds **3–5** were identified by comparison of their spectroscopic features with literature data [7–10].

Table 1 shows the reaction conditions and distribution of oxidation products of **1** in he presence of a range of catalysts under various experimental conditions. Whereas the 3-ethyleneketal derivative of **1** is readily epoxidized by air in the presence of $Ru(O)_2$(tmp) in a β-stereospecific manner (yield 85%, $\beta/\alpha + \beta > 98\%$) [3], compound **1** itself affords no epoxide under the same conditions (Entries 1–3). Instead, a mixture of the epimeric 6-hydroxyketones **3**, **4** and of the diketone **5** is obtained. Although **3** and **4** can be obtained by opening of the 5,6β and 5,6α epoxides of **1**, respectively [15], it seems likely that under the present conditions they derive from the epimeric 6-hydroperoxyketones **6b**, **a**. Indeed, no evidence of epoxide formation could be found by nmr at any stage of the

catalytic process. Moreover, the presence of intermediate peroxidic species was detected in the reaction mixture (see table 1).

Surprisingly, oxidation of **1** was also observed when the stable precursor Ru(CO)(tmp) was substituted for the active species $Ru(O)_2$(tmp). The starting orange solution of Ru(CO)(tmp) gradually turned dark brown by stirring in the presence of **1**, and products **3–5** were obtained (Entry 5). Triruthenium dodecacarbonyl itself was somewhat active as oxidation catalyst of **1** (Entry 8).

Appropriate blank experiments were conducted (Entries 12, 13); no significant amount of any of the oxidation products **3–5** could be detected in the absence of ruthenium porphyrin catalyst, with or without illumination, or in the presence of MnCl(tmp) with or without illumination (Entries 9–10). On the other hand, FeCl(tmp) was found active to some extent as oxidation catalyst of **1**: the yield of oxidation products was only 31% after a day, but surprisingly oxidation at C-6 was highly α-stereoselective (Entry 11). Thus, the presence of a ruthenium porphyrin complex seems essential for efficient oxidation of **1** at room temperature.

Insight into the mechanisms of these ruthenium-catalyzed oxidations was obtained by nmr monitoring the reactions in the presence of Ionol (see table 1). The latter is known to inhibit radical chain reactions by forming stable phenoxyl radicals [16,17]. Addition of Ionol had no effect on the rate of oxidation of **1** in the presence of $Ru(O)_2$(tmp), nor on the distribution of products **3–5** (Entries 2,4). In contrast, oxidation of **1** in the presence of Ru(CO) (tmp) was significantly slowed down by the presence of the phenol: during the first 7 hours after addition of Ionol the orange color of Ru(CO)(tmp) remained unchanged and no trace of oxidation product could be detected, but then solution color change and substrate

Table 1
Products of the ruthenium-porphyrin-catalyzed oxygenation of cholest-5-en-3-one (**1**) [a]

Entry	Catalyst	Reaction time (h)	Product (%) [b]				Unreacted starting material (%) [b]
			(3)	(4)	(5)	(6)	
1	$Ru(O)_2$(tmp)	4	20	12	35		32
2	$Ru(O)_2$(tmp)	24	24	18	39		18
3	$Ru(O)_2$(tmp) [c]	48	26(23)	18(15)	52(21)	(8)	4(0)
4	$Ru(O)_2$(tmp) + Ionol [d]	22	30	17	32		21
5	Ru(CO) (tmp)	53	34	23	39		3
6	Ru(CO) (tmp) + Ionol [d]	4	0	0	0		100
7	Ru(CO)(tmp) + Ionol [d]	22	15	9	12		64
8	$Ru_3(CO)_{12}$	22	13	8	12		67
9	MnCl(tmp)	23	0	0	0		100
10	MnCl(tmp) + light [e]	48	trace	trace	trace		> 95
11	FeCl(tmp)	23	0	12	19		69
12	none	72	0	0	0	trace	100
13	none + light [e]	48	0	trace	trace		> 95
14	Pt [c,f]	24	(20)	(18)	(29)		10

Notes to table 1:

[a] Reaction conditions: substrate 94 mg, catalyst 7.5–10 mg, in benzene 1.5 ml at room temperature under air 1 atm, in the dark unless noted otherwise.

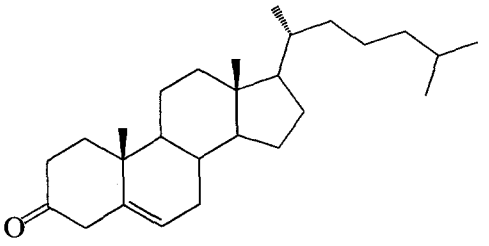
[b] As obtained from ^{1}H nmr of the reaction mixture, unless noted otherwise. Our nmr measurements could not resolve **3** from **6b**, nor **4** from **6a**.

[c] Figures in parentheses refer to % yields of isolated products after preparative tlc on silica; hydroperoxides **6** were characterized by R_f measurements and positive analytical tests for peroxide.

[d] 2,6-di-tert-butyl-4-methylphenol, 0.5 mol/mol of catalyst.

[e] Tungsten lamp.

[f] Ref. [10].



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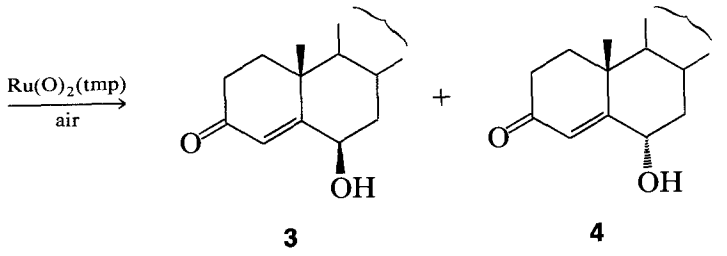
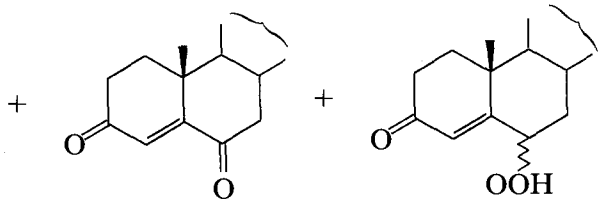


3 **4**

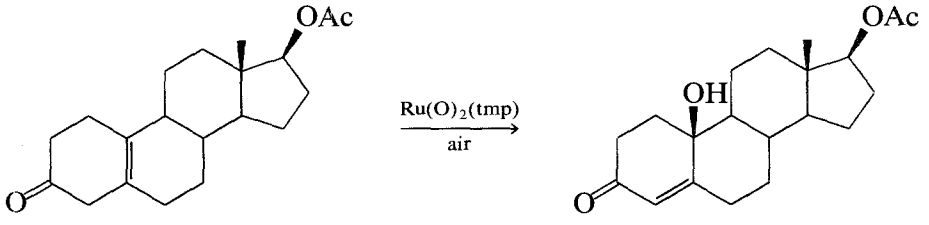


5 **6a,b**
a: α-OOH
b: β-OOH

oxidation occurred as in the presence of Ru(CO)(tmp) alone. These observations establish the non-radical nature of the $Ru(O)_2$(tmp)-catalyzed oxidation of **1**, and the radical character of the early stages of the Ru(CO)(tmp)-catalyzed process.

Apparently, the β,γ-unsaturated ketone **1** is exceedingly sensitive to oxygenation. Even in the absence of catalyst, it undergoes incipient autoxidation to the hydroperoxy species **6** in small amounts (undetectable by ^{1}H nmr) which nevertheless can be isolated by tlc (Entry 12). We have checked that the latter are able to oxidize Ru(CO)(tmp) to a brown species similar to $Ru(O)_2$(tmp). The presence of the latter is substantiated by our observation that cholesteryl acetate is β-stereospecifically epoxidized to some extent by this reaction mixture. Therefore, we assume that oxidation of Ru(CO)(tmp) by **6** involves intermediate radical and/or paramagnetic ruthenium species which are quenched in the presence of Ionol. The $Ru(O)_2$(tmp)-catalyzed and Ru(CO)(tmp)-catalyzed oxidation processes would follow similar reaction paths as soon as the $Ru(O)_2$(tmp) active species is formed in the latter case.

The estr-5(10)-ene-3-one derivative **2** was added to a C_6D_6 solution of $Ru(O)_2$(tmp) generated in situ by reaction of mCPBA with Ru(CO)(tmp) [3], and the resulting solution was stirred under air for 21 hours. Monitoring by tlc indicated that the reaction reached completion in 7 hours. The products were separated by preparative tlc on silica gel. The main product was isolated in 42% yield, and it was identified as the 10β-hydroxy derivative **7**. The corresponding 10α-hydroxy derivative could not be detected by nmr in the reaction mixture; if present, it would account to less than 1% of the products. Several other low-abundant products were detected by tlc, accounting to an overall yield of ca. 10–15%, but they were not identified.



2 **7** (42%)

The structure of **7** was assigned on the basis of accurate mass spectrometric data (calculated, 332.1989; found, 332.2003) and by comparison of its ^{1}H and ^{13}C nmr spectra with those of related compounds. The chemical shift of the C-18 methyl protons of **7** (0.84 ppm) is close to that found in the known [12] 10β,17β-dihydroxy-estr-4-ene-3-one (0.83 ppm), and different from that of 10α,17β-dihydroxy-estr-4-ene-3-one [12] (0.70 ppm). Moreover, the ^{13}C chemical shifts of C-4 (124.9), C-5 (163.7), and C-10 (69.9) in **7** are nearly identical to those (124.99, 163.69, and 70.35, respectively) of 10β-hydroxy-estr-4-ene-3,17-dione [18].

3. Experimental

REAGENTS

Cholest-5-ene-3-one was purchased from Fluka. This product showed eight spots on tlc, and therefore it was purified by column chromatography on silica gel using as eluent a mixture of ethyl acetate and petroleum ether (30/70). The eluate was pure, as judged by 200 MHz ^{1}H nmr, and tlc ($R_f = 0.81$, eluent ethyl acetate/cyclohexane, 30/70); however two minor spots ($R_f = 0.40$ and 0.33) were visible after spraying the plate by a Kagi-Mischer modified reagent [3]. These impurities were identified as the 6-hydroperoxy species **6** (see table 1). The product was used at this stage of purity. 17β-acetoxy-estr-5(10)-ene-3-one was prepared by acetylation of the parent alcohol. The latter, 17β-hydroxyestr-5(10)-ene-3-one, was obtained according to the literature [11,12]. Meso-tetramesityl-porphyrin was obtained by the Rothemund method [19], and its manganese(III) and iron(III) complexes were prepared by the Adler method [20]. Ru(CO)(tmp) was prepared from the porphyrin free base as previously described [21]. $Ru(O)_2$ (tmp) was prepared from the latter by mCPBA oxidation [14].

METHODS

^{1}H and ^{13}C nmr spectra were run with a Bruker AC200 spectrometer on C_6D_6 solutions with TMS as internal standard.

CATALYTIC OXYGENATION OF CHOLEST-5-ENE-3-ONE

General procedures for catalytic oxidation, product detection and isolation have been detailed in previous papers [3,6]. Specific reaction conditions for cholest-5-ene-3-one are shown in Table 1. The reaction was monitored by ^{1}H nmr, and the distribution of products **3–5** was calculated by integration of the peaks of the ethylenic protons. Product isolation was performed by tlc on silica gel plates (20×20 cm^2, 0.5 mm thickness). Spectroscopic features of the products **3–5** were identical with literature data [7–10].

17β-ACETOXYESTR-5(10)-ENE-3-ONE **2**

1 g of 17β-hydroxyestr-5(10)-ene-3-one was dissolved in 10 mL of pyridine and 7.3 mL of acetic anhydride were added. The mixture was stirred at room temperature for 4 hours, after which the solvent and reagent were removed azeotropically with toluene. Purification of the product was obtained by column chromatography on silica gel. Elution was performed with mixtures of petroleum ether and diethyl ether of increasing polarity. Yield 666 mg (57%). MP 144–145 °C. Mass spectrometry (EI): $M^{\cdot+}$ 316.2029, calculated 316.2038. ^{1}H nmr (C_6D_6, δ ppm/TMS): 0.77 (s, 18-CH_3); 1.75 (s, CH_3CO); 2.50 (s, H-4); 4.74 (t, H-17). ^{13}C nmr (C_6D_6, δ ppm/TMS): 12.5 (18-CH_3); 82.6 (C-17); 126.6, 130.8 (C-5, C-10); 170.1 (CO-CH_3); 208.1 (C-3).

17β-ACETOXY-10β-HYDROXYESTR-4-ENE-3-ONE **7**

100 mg (3.16×10^{-4} mol) of **2** and 11.5 mg (1.26×10^{-5} mol) of Ru(CO)(tmp) were dissolved in 3 mL of C_6D_6. 5.5 mg (3.16×10^{-5} mol, 2.5 equiv/Ru) of mCPBA were added, and the resulting solution was stirred under air for 21 hours. The reaction mixture was then chromatographed on two silica gel plates (20×20 cm^2, 1 mm thickness), using cyclohexane-ethyl acetate 70 : 30 as eluent, and 44 mg of **7** were isolated. Yield 42% MP 177–179°C. Mass spectrometry (EI): $M^{\cdot+}$ 332.2003, calculated 332.1989. ^1H nmr (C_6D_6, δ ppm/TMS): 0.84 (s, 18-CH_3); 1.72 (s, CH_3CO); 4.72 (t, H-17); 5.78 (s, H-4). ^{13}C nmr (C_6D_6, δ ppm/TMS): 12.2 (C-18); 82.6 (C-17); 124.9, 163.7 (C-4, C-5); 170.3 (CH_3CO); 197.8 (C-3); 69.9 (C-10).

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