STEREOSELECTIVE 7α-HYDROXYLATION OF 3β-ACETOXY-Δ^5-STEROIDS BY $Fe(PA)_3/H_2O_2/MeCN$

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Stereoselective 7α-hydroxylation reaction of Δ^5-steroids by a Fe(PA; picolinate)$_3$/H_2O_2/MeCN system is presented. The 7α-hydroxylation reactions were achieved in 33-40% yields by addition of 30%-H_2O_2 to a solution of 3β-acetoxy–Δ^5-steroids **1a-1d** and a crystalline of $Fe(PA)_3$ in MeCN.

KEY WORDS oxygenation; 7 α-hydroxylation; $Fe(PA)_3/H_2O_2$/MeCN; Δ^5-steroid; Gif system

Stereoselective 7α-hydroxylation of 3β-acetoxy-Δ^5-steroids is interesting in terms of the syntheses of recently discovered cytotoxic 3β,7α-dihydroxy-Δ^5 -steroids [1] and the metabolism of cholesterol by the cytochrome P-450 species 7α-hydroxylase in the livers of most mammalians. Many investigations on oxygenation reactions using simple, readily available reagent systems mimicking mono-oxygenase enzymes have been carried out. Of those, a study on iron(II) or iron(III) picolinate (PA) complexes as a catalyst of oxygenation reactions raised challenging problems. It was also noted that the oxidation reaction with H_2O_2 catalyzed by iron picolinate complexes varied depending on the solvents used. [2] Although many studies on iron picolinate complex /H_2O_2/solvent systems have been reported by the Sawyer group[2] and Barton group,[3] there has been no report to date on the oxidation reaction by the $Fe^{III}(PA)_3/H_2O_2$/MeCN system. We report that the modified system $Fe(PA)_3/H_2O_2$/MeCN as an alternative to the Gif system reagent is effective in stereoselective 7α-hydroxylation of 3β-acetoxy-Δ^5 steroids **1a-1d.**

The oxygenation reactions with this system of 3β-acetoxy-Δ^5-steroids, cholesterol acetate (**1a**), stigmasterol acetate (**1b**), pregnenolone acetate (**1c**), and dehydroisoandrosterone acetate (**1d**) were carried out according to the procedure shown in Table 1. The above reaction gave 7α-hydroxy derivatives **2** (33-40%yields) along with a trace amount of 7β-hydroxy derivatives **3**, 7-oxo derivatives **4** (16-23% yields), α and β epoxides mixtures **5** and **6** (3-13% yields), and recovered materials in all cases (Chart 1). The structural identification of **2** and **3** was done by comparing the physical data of the corresponding dihydroxy compounds prepared by hydrolysis with those of the respective authentic samples, [4a,b,c] respectively. The structure of **4**, **5**, and **6** was identified by comparison of the physical data with those of the respective authentic samples.[4b,d,e] In this investigation, we found that the most efficient and stereoselective 7α-hydroxylation reaction was obtained in all cases using a molar ratio of substrate **1** : $Fe(PA)_3$: 30% H_2O_2 = 1 : 0.5 : 3.

The reaction mechanism with substrates **1a-1d** using the present reagent system can be postulated as shown in Chart 2, and the complexes circulate in the order of (**B**)→(**C**)→(**D**)→(**E**) or (**F**)→→(**B**). Preferential 7-hydroxylation compared to 7-ketonization may be due to the greater formation of (**E**) relative to (**F**) as a result of the sufficient H_2O contained in 30% H_2O_2.

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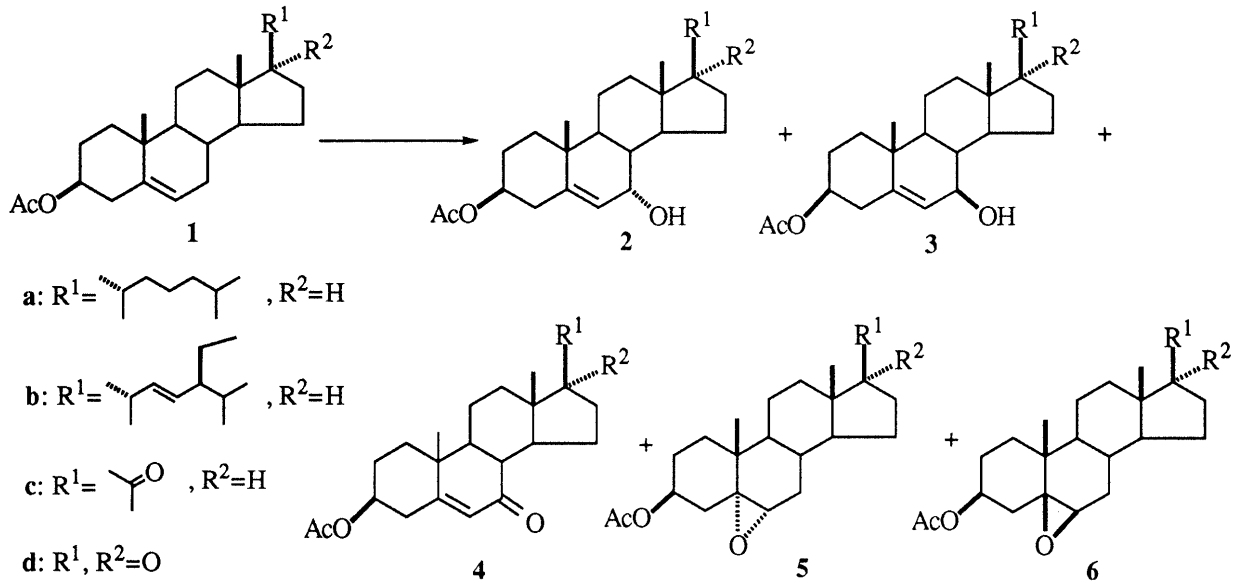

Chart 1

Table 1. Oxygenation of Δ^5-Steroids **1a-1d** with $Fe(PA)_3/H_2O_2$ /MeCN [a,b]

Run	Substrate	Product (yield, %) [c]					Recovery (%)	Mass balance (%)
		2 7α-Hydroxy	**3** 7β-Hydroxy	**4** 7-Oxo	**5** α-Epoxy	**6** β-Epoxy	**1**	
1	**1a**	**2a** (40.0)	**3a** (1.1)	**4a** (19.8)	**5a** (4.7)	**6a** (8.4)	22.6	96.6
2	**1b**	**2b** (36.5)	**3b** [d]	**4b** (23.1)	**5b** (4.8)	**6b** (6.1)	24.7	95.2
3	**1c**	**2c** (33.1)	**3c** [d]	**4c** (15.7)	**5c** (3.3)	**6c** (3.4)	19.9	75.4
4	**1d**	**2d** (39.3)	**3d** [d]	**4d** (22.0)	**5d** (0.7)	**6d** (1.9)	19.8	83.7

[a] The iron complex $Fe(PA)_3$ (**B**) can be prepared conveniently by the reaction of $Fe^{III}(ClO_4)_3 \cdot 9H_2O$ (1 mol) with sodium picolinate (3 mol) in water in 93% yield, followed by recrystallization with MeOH, changing it to the hydrous form, $Fe(PA)_3(H_2O)$ (**A**). By exposure to moisture in air , it exists as a mixture of the hydrous and anhydrous form in wet MeCN; [b] Typical reaction procedure: to a solution of substrate (1 mmol) and $Fe(PA)_3$ (0.5 mmol) in MeCN (70 ml) were added three 0.1s-ml portions of 30% aqueous H_2O_2 (0.3 ml, 3 mmol) every 30 min at room temperature and the reaction mixture was stirred for 3 h at room temperature. [c] Isolated yields based on substrates (**1**). [d] Trace amounts (<0.5%).

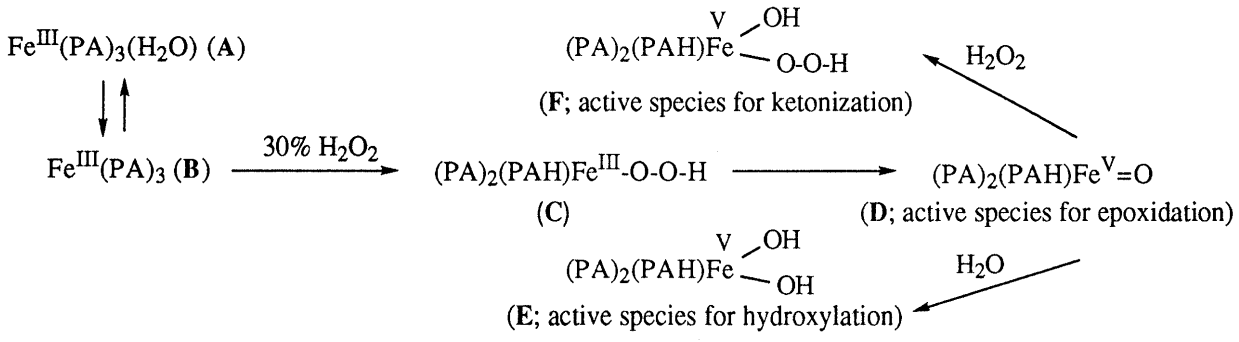

Chart 2. Proposed Active Species in $Fe^{III}(PA)_3/H_2O_2$ /MeCN System

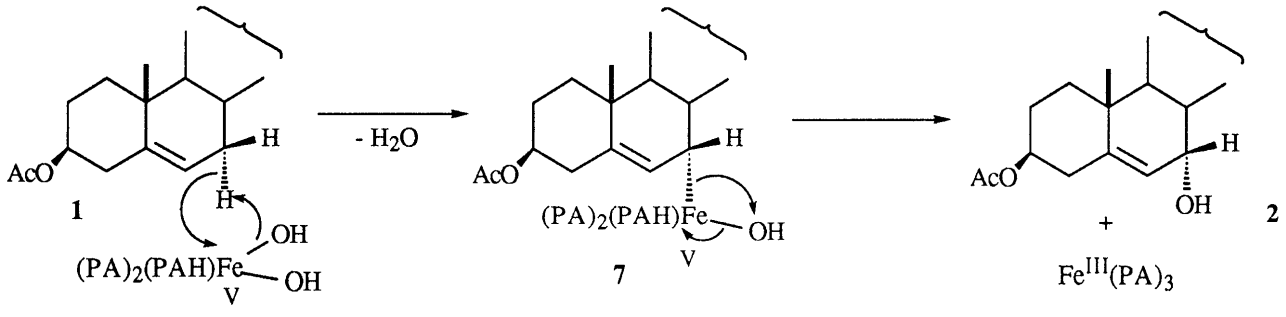

Chart 3. Proposed Mechanism for 7α-Hydroxylation of Δ^5-Steroids

The mechanism of stereoselective 7α-hydroxylation for the formation of **2** can be postulated to be as follows (Chart 3). The σ bond formation between the C-7α-position in **1** and Fe^V atom in (**E**) as a hypothetically active species with nonradical pathways [3] may take place stereoselectively to yield **7** under the stereoelectronic effect [5] and steric hindrance. Further, the cleavage of the σ bond between the Fe atom and the C7-position in **7** including the rearrangement of the hydroxy group, may proceed to permit **2** to retain its configuration. On the other hand, the possibility of participation of an active species Fe^V=O (**D**) in 7α-hydroxylation cannot be excluded.

Subsequently, we investigated the reaction of **1a** with the Gif system ($GoAgg^{III}$; $FeCl_3 \cdot 6H_2O$-PAH/H_2O_2/HOAc-pyridine) to compare it with the reaction with this modified system. Although reaction of **1a** with the above Gif reagent system gave only a 7-oxo derivative **4a** in 4% yield, it did not proceed for 7-hydroxy derivatives **2a** and **3a**. Furthermore, it was reported that the reactions of cholesterol acetate **1a** using known the allylic acetoxylation reagents, CuBr/*tert*-BuOOCOPh/HOAc,[1] $Pd(OAc)_2/Fe(NO_3)_3 \cdot 9H_2O/O_2$/HOAc,[6] and $Pb(OAc)_4$/HOAc [7] gave 3β,7α- and 3β,7β-diacetoxy-5-cholestene in almost same amount as the α and β forms, with about 20% yields.

These results provide a new example of oxidative 7α-hydroxylation of Δ^5-steroids, one of the major metabolic reactions catalyzed cytochrome P-450, in this model system for mono-oxygenase.

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