

**CHLOROIRON(III)-5,10,15,20-TETRAARYLPORPHINATE/N-METHYLIMIDAZOLE CATALYZED
OXIDATION OF ANDROST-4-EN-3,17-DIONE BY CUMENE HYDROPEROXIDE**

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Summary: The oxidation of androst-4-en-3,17-dione with cumene hydroperoxide, catalyzed by chloroiron(III)-5,10,15,20-tetraarylporphinate/N-methylimidazole systems, was studied under different reaction conditions. The chloroiron(III)-5,10,15,20-tetra(2,6-dichlorophenyl)porphinate/N-methylimidazole system in dichloromethane was found to be the most effective system for the aromatization of the A ring of androst-4-en-3,17-dione.

Cytochrome P-450 aromatase is a member of the monooxygenase family of heme enzymes¹. The biotransformation of androgens to estrogens is catalyzed in vivo by microsomal cytochrome P-450 aromatase, utilizing three moles each of NADPH and oxygen². The high-valent iron(IV)-oxo intermediate, formed by the reductive activation of molecular oxygen by cytochrome P-450³, is responsible for the in vivo oxidation of androst-4-en-3,17-dione(1) to 19-hydroxyandrost-4-en-3,17-dione(2), androst-4-en-3,17,19-trione(3) and estrone(4). These high-valent iron(IV)-oxo intermediates⁴ are also formed by the reaction of iron(III) porphyrins with different monooxygen donors and are responsible for the hydroxylation of hydrocarbons⁵, epoxidation of olefins⁶, oxidation of heteroatoms⁷ and the cleavage of C-C bonds⁸ in organic substrates. We report here the oxidation of 1 and other related androgens by cumene hydroperoxide(CumOOH)⁹, catalyzed by different chloroiron(III)-5,10,15,20-tetraarylporphinate [TAPFe(III)Cl]/N-methylimidazole (N-MeIm) systems under different reaction conditions.

In a typical case, the oxidation of 1 by CumOOH catalyzed by Cl₈TPPFe(III)Cl in dichloromethane gave 2 and 3 in 2.7 and 1.5% yields respectively. Further, the same oxidation when carried out in the presence of N-MeIm gave 2, 3, and 4 in 31.3, 15.7 and 32.1% yields respectively. The results of the oxidation of 1 with CumOOH catalyzed by different TAPFe(III)Cl/N-MeIm systems are given in the Table.

The different products were identified by comparing the R_f values¹⁰ and h.p.l.c. retention times with those of authentic samples (Table). In a

typical example, 1 (200 mg, 0.7 mmol) was oxidized using the $\text{Cl}_8\text{TPPFe(III)-Cl}$ (7.0 mol)/N-MeIm (70.0 mol)/CumOOH (0.2 mmol) system and, after work-up, estrone was isolated by preparative t.l.c.¹⁰ in 5.8% yield (10 mg). The identity of the isolated estrone was confirmed by spectroscopic comparison¹¹.

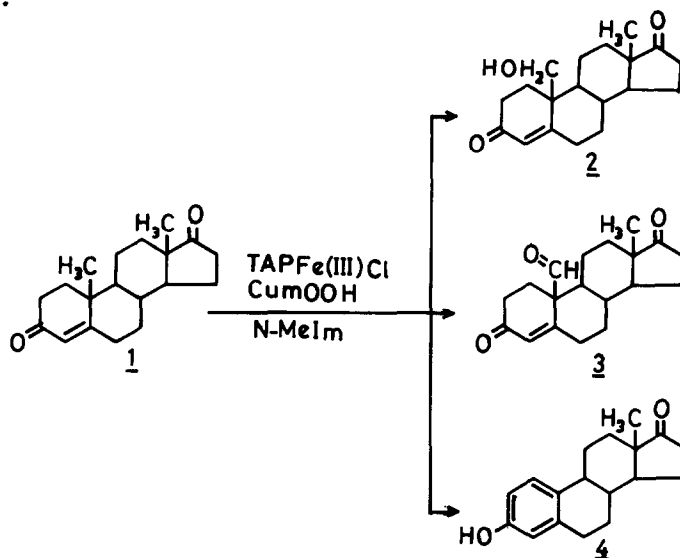


TABLE: OXIDATION PRODUCTS^a OF 1 WITH DIFFERENT IRON(III)PORPHYRINS/CumOOH SYSTEMS^b

S.No.	Catalyst	Substrate	Yield		
			<u>2</u>	<u>3</u>	<u>4</u>
1.	$\text{Cl}_8\text{TPPFe(III)Cl}$	<u>1</u>	2.7	1.5	-
2.	$\text{Cl}_8\text{TPPFe(III)Cl/N-MeIm}$	<u>1</u>	31.3	15.7	32.1
3.	$\text{TPPFe(III)Cl/N-MeIm}$	<u>1</u>	-	37.5	-
4.	$\text{Me}_{12}\text{TPPFe(III)Cl/N-MeIm}$	<u>1</u>	-	14.3	1.8
5.	$\text{Cl}_8\text{TPPFe(III)Cl/N-MeIm/CH}_3\text{OH}$	<u>1</u>	31.3	6.5	-
6.	$\text{Cl}_8\text{TPPFe(III)Cl/N-MeIm}$	<u>2</u>	-	4.3	52.5
7.	$\text{Cl}_8\text{TPPFe(III)Cl/N-MeIm}$	<u>3</u>	-	-	12.3

a: Relative yields estimated by h.p.l.c. H.p.l.c. conditions: Zorbax ODS column (reversed phase, 15 cm x 4 mm i.d.); acetonitrile solvent (0.4 ml/min.); UV detector (260 nm); retention times (min.): 1, 7.6; 2, 6.4; 3, 4.9 and 4, 5.7.

b: Reaction conditions: substrate (35 mol):porphyrin:CumOOH:N-MeIm in the ratio 100:1:25:10 and the reactions were carried out in dry dichloro-methane at 25°C for 12 h.

The reaction of TAPFe(III)Cl with CumOOH is slow and is accelerated in the presence of N-methylimidazole¹². Firstly, N-MeIm axially ligates to the iron atom by displacing the chloride. Secondly, it acts as an acid-base catalyst for the heterolytic cleavage of the O-O bond of the porphyrin-Fe-O-O-Cumyl molecule to form iron(IV)-oxo intermediates [TAPFe(IV)=O]^{13,14}. This [TAPFe(IV)=O] converts 1 to 2 either by a concerted pathway or by hydrogen abstraction from the 19-methyl group of 1 to form a 19-radical and [TAPFe(IV)OH], followed by an oxygen-rebound¹⁵ hydroxy radical transfer from [TAPFe(IV)OH] to give 2. The dehydrogenation of primary alcohols to aldehyde is a known reaction of high-valent iron complexes¹⁶. The iron(IV)-oxo intermediates formed by the Cl₈TPPFe(III)Cl/N-MeIm system may be responsible for the conversion of 3 to 4. Recently, a similar oxidation of 3 to 4 using the F₂₀TPPFe(III)Cl/KO₂/18-crown-6 system in acetonitrile followed by acid treatment¹⁷, and the aromatization of some methyltetralones by using F₂₀TPPFe(III)Cl/C₆H₅IO in dichloromethane followed by acid treatment¹⁸, have been achieved. The aromatization of 1 has been observed only in dichloromethane. No aromatization was observed when the solvent contained small quantities of methanol or water. Thus, the present study indicates that the Cl₈TPPFe(III)Cl/N-MeIm/CumOOH system is a suitable model for microsomal cytochrome P-450 aromatase.

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9. Abbreviations used: CumOOH: cumene hydroperoxide; N-MeIm: N-methylimidazole; TAP: 5,10,15,20-tetraarylporphin; TPP: 5,10,15,20-tetra-phenylporphin; Me₁₂TPP: 5,10,15,20-tetra(2,4,6-trimethylphenyl)porphin; Cl₈TPP: 5,10,15,20-tetra(2,6-dichlorophenyl)prophin; F₂₀TPP: 5,10,15,20-tetra(pentafluorophenyl)prophin.

10. T.l.c. conditions: silica gel plates (5 cm x 20 cm or 10 cm x 20 cm), 1 mm thickness; solvent system: petroleum ether(60-80°)-ethyl acetate (1:1); 0.5% vanillin in ethanol-H₂SO₄ (1:4) spraying agent; baking at 110°C for 10 min. 1(R=0.32):red, 2(R_f=0.20);grey, 3(R_f=0.28);red and 4(R_f=0.47): purple.
11. M.p. 246-249°C (lit.¹⁹ m.p. 249-253°); UV(methanol): 282.0 nm (mM, 2.4); [α]_D³⁰:+160.0°(dioxan, 0.2); IR(nujol): 3350, 1710, 1620, 1580, 1280, 1240, 920, 880, 720 and 660 cm⁻¹; ¹H NMR(CDCl₃): 0.90(s, 3H, 18-CH₃), 1.45-2.90(m, 15H, skeletal-H), 4.70[s, 1H, 3-OH(exch.)], 6.58(d, J_{2,4}=3 Hz, 1H, 4-H), 6.64(dd, J_{1,2}=9 Hz & J_{2,4}=3 Hz, 1H, 2-H) and 7.15(d, J_{1,2}=9 Hz, 1H, 1-H); M.S.(EI, 70 eV) m/z(rel. int.): 271(M+1, 18.2), 270(M⁺, 100), 242(3.2), 214(10.2), 213(19.4), 199(4.8), 185(34.4), 172(27.4), 160(17.5) and 146(34.4).
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