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Note

Oxidation of phenylbutazone with hydrogen peroxide catalyzed by 5,10,15,20-tetraaryl-porphyrinatoiron(III) chlorides in dichloromethane

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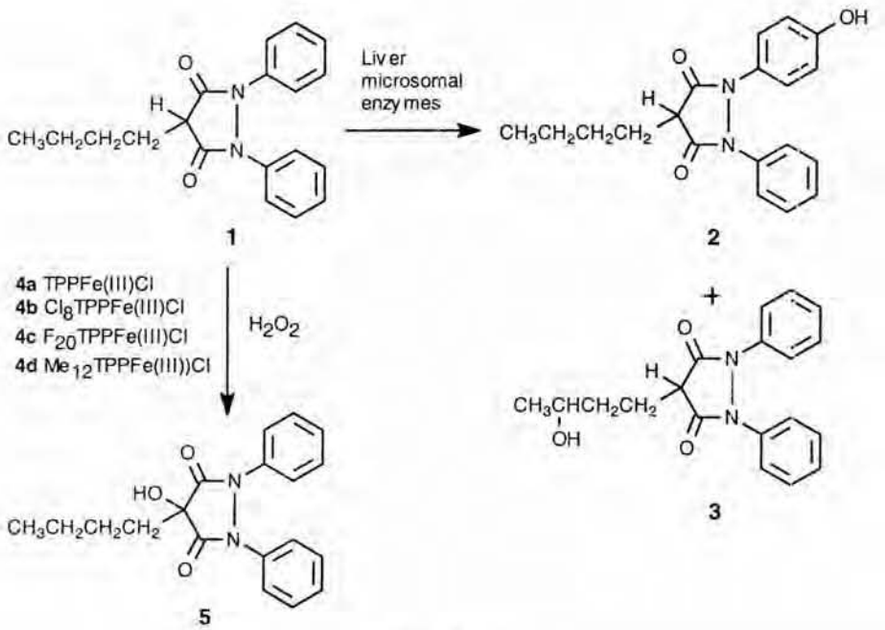
Oxidation of phenylbutazone with hydrogen peroxide catalyzed by 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides in dichloromethane gives a new product 4-hydroxyphenylbutazone in moderate yields.

Phenylbutazone (4-*n*-butyl-1,2-diphenylpyrazolidine-3,5-dione) **1** is an important anti-inflammatory drug, and is metabolized to oxyphenbutazone **2** and γ-hydroxyphenylbutazone **3** by liver microsomal enzymes[1-5]. The biomimetic oxidation of the selected drug **1** with monooxygen donor catalyzed by 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides ($TAPFe^{III}Cl$) **4a-d** has been studied to understand the drug metabolism without the use of experimental animals[6-9]. Herein, we report the biomimetic oxidation of phenylbutazone with hydrogen peroxide catalyzed by $TAPFe^{III}Cl$ in an organic solvent with an aim to understand the reactions of natural Cytochrome P450 enzyme.

The reaction of phenylbutazone **1** with hydrogen peroxide catalyzed by 5,10,15,20-tetraphenyl-porphyrinatoiron(III) chloride ($TPPFe^{III}Cl$) **4a** in dichloromethane after 1 hr did not give the normal metabolites oxyphenbutazone **2** and γ-hydroxyphenyl-butazone **3**, instead it gives a 4-hydroxyphenylbutazone (4-hydroxy-4-*n*-butyl-1,2-diphenylpyrazolidine-3,5-dione) **5** (cf. **Scheme I**) in 15.3% yield. The appearance of a band at 3370 cm^{-1} in the IR spectrum of the product **5** indicate the presence of an OH group. The absence of 4-H peak at δ 3.37 and the presence of an 4-OH (brs) peak at 3.3 ppm together with the change in the multipliticity of Bu-4′-CH_2 protons at δ 2.0 ppm to a triplet in the ^1H NMR spectrum confirms the formation of **5**.

The oxidation of **1** with hydrogen peroxide in dichloromethane after 1 hr of stirring at room temperature in an atmosphere of N_2 using TPPFe(III)Cl **4a** in the presence of *N*-methylimidazole (*N*-MeIm), $Cl_8TPPFe(III)Cl$ **4b**, $F_{20}TPPFe(III)Cl$ **4c**



Scheme I

and Me_{12}TPPFe(III)Cl **4d** gave the desired product **5** in 20.5%, 35%, 39% and 31.2% yields, respectively.

Abstraction of hydrogen radical from the highly acidic 4-position of phenylbutazone by the high valent oxo-iron(IV)porphyrins and subsequent recombination of phenylbutazone radical with the hydroxy radical or hydroxy-iron(III)porphyrin present in the reaction medium could be a possible explanation for the formation of 4-hydroxyphenyl-butazone. This type of hydrogen abstraction and recombination mechanism has been reported earlier with the Cytochrome P450 chemical model systems[10].

Experimental Section

General. Melting points were determined on a Thomas Hoover Unimelt capillary melting apparatus and are uncorrected. Electronic spectra were recorded on a Shimadzu UV 260 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrophotometer(ν_{max} in cm^{-1}). ^1H NMR spectra were recorded on a Bruker 300 MHz spectrophotometer. Electron induced mass spectra(EIMS) were recorded on a Jeol SX102/DA-6000 (6 kV, 10 mA) spectrophotometer. HPLC analyses were on a photodiode array based Waters HPLC (Model 991, μ-Bondapak C_{18} reverse phase column, 3.9×300 mm) using methanol as eluent at a flow rate of 0.1 mL/min, monitored at 280 nm. HPLC retention times of phenylbutazone **1** and 4-hydroxyphenylbutazone **5** are 18.1 min and 31.6 min, respectively. The ratio of substrate : oxidant : catalyst used was 100 : 10 :1.

Materials and methods

Phenylbutazone **1** was prepared by the condensation of diethyl *n*-butylmalonate with 1,2-diphenylhydrazine in the presence of sodium methoxide following the literature procedure[2].

Hydrogen peroxide (30%) was obtained from S.D. Fine Chemicals, India. The catalysts **4a-d** were prepared by reaction of the corresponding benzaldehyde with pyrrole by minor modification of the literature procedures[11,12].

Isolation and characterization of oxidation products of phenylbutazone 1 with hydrogen peroxide catalyzed by 4a-d. Aqueous hydrogen peroxide (0.1 mmole, 30%, 11.2 μL) was added to a mixture of phenylbutazone **1** (1 mmole, 300 mg) and $Cl_8TPPFe^{III}Cl$ **4b** (0.01 mmole, 12.0 mg) in dichloromethane (10 mL). The reaction mixture was stirred for 1 hr at room temperature under N_2 atmosphere. Column chromatograpy of the reaction mixture over silica gel afforded 95 mg (30% yield) of **5**, mp 124-127 °C; UV (CH_3OH): 226 (log ε 1.5) and 244 (1.4) nm; IR (KBr): 3370 (OH), 2958, 2931, 2871, 1756, 1705, 1596, 1491, 1465, 1362, 1296, 1275, 1196, 1175, 1158, 1093, 1026, 908, 824, 759, 744, 692, 639, 504, 447 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.3 (brs, 1H, OH), 7.16-7.34 (m, 10H, Ar-H), 2.02-2.08 (t, 2H, Bu-4′-CH_2), 1.25-1.45 (m, 4H, Bu-3′ and 2′-CH_2), 0.9 (t, 3H, Bu-1′-CH_3); EIMS: m/z 324 (M^+).

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