Tungstate-catalysed Oxidation of Tetrahydroquinolines with Hydrogen Peroxide: a Novel Method for Synthesis of Cyclic Hydroxamic Acids

Shun-Ichi Murahashi,* Tetsuya Oda, Toshiaki Sugahara, and Yoshiyuki Masui

Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka, 560, Japan

Tungstate-catalysed oxidation of 1,2,3,4-tetrahydroquinolines with hydrogen peroxide gives 1-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolines highly efficiently.

Hydroxamic acids are an increasingly important class of compounds with respect to their utility as synthetic intermediates, their biological activity, and their strong chelating ability.[1]

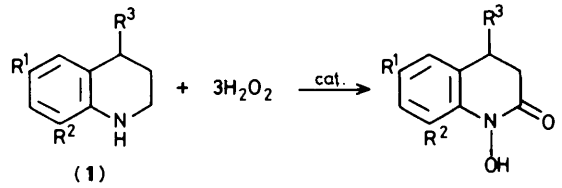
We report here a new type of oxidation of cyclic amines with hydrogen peroxide to give hydroxamic acids as depicted in Scheme 1. The substrates can be obtained readily by selective reduction of quinolines[2] (derived from coal and oil shales), and the hydroxamic acids thus obtained are biologically active and can be readily converted into various key synthetic intermediates.

The conversion of 1,2,3,4-tetrahydroquinoline (**1a**) into 1-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline (**2a**), which shows antibacterial activity,[3] is a typical example. To a mixture of (**1a**) (8.16 g, 0.062 mol) and sodium tungstate (0.20 g, 0.60 mmol) in methanol (750 ml) was added aqueous 30% hydrogen peroxide (36 ml; 0.36 mmol) with stirring at 0 °C under argon. The mixture was stirred at room temperature overnight. After removal of methanol under reduced pressure, the residue was extracted with dichloromethane. Removal of the solvent gave the crude hydroxamic acid (**2a**) (9.7 g, 97%). Short-column chromatography on silica gel eliminated a small amount of contaminated quinoline and gave analytically pure (**2a**) in 84% yield, m.p. 117—118 °C, ^{1}H n.m.r. ($CDCl_3$) δ 2.78 (t, *J* 6.0 Hz, 2H), 2.83 (t, *J* 6.0 Hz, 2H), 6.82—7.58 (m, 4H), and 8.55 (br, 1H).

The effect of changing reaction conditions on the oxidation of (**1a**) was studied. Sodium tungstate is the most effective catalyst; others such as H_2WO_4, Na_2MoO_4, $MoO_2(acac)_2$, $VO(acac)_2$ (acac = pentane-2,4-dione) and CeO_2 gave poor yields of hydroxamic acids.[3] Methanol is the best solvent. With a non-polar solvent, such as dichloromethane, the hydroxamic acid (**2a**) was obtained in 60—80% yield in the presence of phase-transfer catalysts such as methyltrioctylammonium chloride and cetyltrimethylammonium chloride.

Representative results for the formation of various cyclic hydroxamic acids are summarized in Table 1. The present method is the first to be generally applicable for the synthesis of such hydroxamic acids, although there are few specific methods which involve reductive cyclization of *o*-nitrophenylpropionic acids and derivatives.[3,4] The substrates can be obtained readily by selective hydrogenation of the corresponding quinolines under water-gas shift reaction conditions.[2]

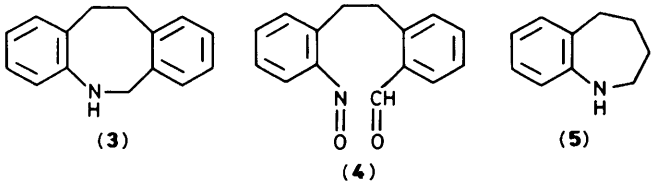
The oxidation of 5,6,11,12-tetrahydrodibenz[*b*,*f*]azocine (**3**) gave 2-[2-(2-nitrosophenyl)ethyl]benzaldehyde (**4**) (31%, m.p. 41—41.5 °C). Oxidation of 2,3,4,5-tetrahydrobenz[*b*]-azepine (**5**) gave (**2a**) (33%) along with unchanged (**5**) (23%).



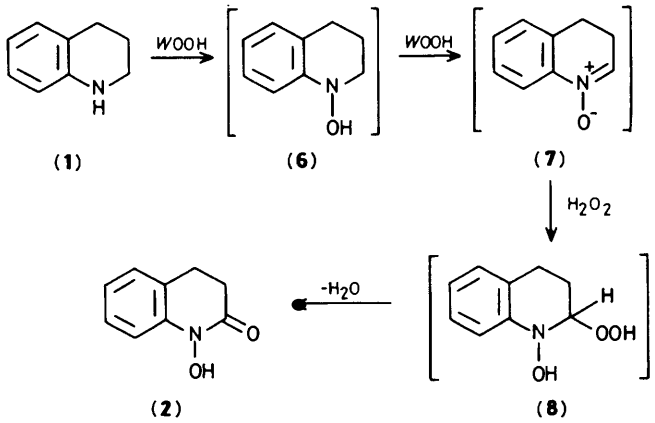
(**1**)

(**2**) **a**; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^2 = H$, $R^3 = Me$
c; $R^1 = Me$, $R^2 = R^3 = H$
d; $R^1 = OMe$, $R^2 = R^3 = H$
e; $R^1 = NHAc$, $R^2 = R^3 = H$
f; $R^1 = Cl$, $R^2 = R^3 = H$
g; $R^1 = Ac$, $R^2 = R^3 = H$
h; $R^1 = R^3 = H$, $R^2 = Me$

Scheme 1



(**3**) (**4**) (**5**)



(**1**) (**6**) (**7**) (**8**) (**2**)

Scheme 2. $W = WO_3^-$, WO_4^-, or WO_6^-.

Table 1. Catalytic oxidative transformation of tetrahydroquinolines (**1**) to hydroxamic acids (**2**).[a]

Hydroxamic acid[b]	Isolated yield (%)[c]
(**2a**)	84
(**2b**)	83
(**2c**)	82
(**2d**)	83
(**2e**)	85
(**2f**)	58
(**2g**)	52
(**2h**)	57

[a] Carried out as described in the text. [b] The structures of the products were determined on the basis of analytical and i.r., n.m.r., and mass spectral data. [c] Analytically pure products.

The present reaction can be rationalized in terms of Scheme 2. *N*-Oxidation of 1,2,3,4-tetrahydroquinolines with tungstate peroxy acid (*W*OOH; $W = WO_3^-$, WO_4^-, or WO_6^-) derived from sodium tungstate and hydrogen peroxide gives hydroxylamines (**6**), which undergo further oxidation to nitrones (**7**).[5] The nucleophilic reaction of the unstable nitrones (**7**) with hydrogen peroxide gives the hydroperoxides (**8**), which undergo dehydration to hydroxamic acids (**2**).

Work is in progress to investigate the mechanism of the reaction and to apply the method to the synthesis of biologically active 3,4-dihydrocarbostyrils and other systems.

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