reaction mixture was stirred for 4 h at ambient temperature. To the mixture was added a saturated aqueous ammonium chloride solution (50 mL) and ether (50 mL). The organic layer was separated, and the aqueous layer was extracted with ether (50 mL). The combined organic layers were dried over sodium sulfate. Removal of the solvent and column chromatography (SiO_2, dichloromethane) gave hydroxylamine **27** (1.40 g, 67%): IR (neat) 3400, 3080, 1605, 1570, 1460, 1335, 1265, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.87-3.39 (m, 4 H, $-CH_2-$), 4.76 (s, 1 H, ArCHN), 6.88-7.88 (m, 10 H, ArH and OH).

6-(Benzyloxy)-2-hydroxy-7-methoxy-1-[2,3-(methylenedioxy)benzyl]-1,2,3,4-tetrahydroisoquinoline (28). To a mixture of magnesium turnings (0.352 g, 14.5 mmol) and THF (5 mL) were added dropwise a solution of 2,3-(methylenedioxy)benzyl bromide (2.97 g, 13.8 mmol) in THF (20 mL) and nitrone **6** (0.617 g, 2.18 mmol) in THF (10 mL) dropwise at room temperature, and the reaction mixture was stirred for 5 h. To the mixture were added a saturated aqueous ammonium chloride solution (20 mL), water (10 mL), and chloroform (30 mL). The organic layer was separated, and the aqueous layer was extracted with chloroform (30 mL × 2). The combined organic layers were dried over magnesium sulfate. Removal of the solvent and column chromatography (SiO_2, 3:1 hexane/ethyl acetate) gave hydroxylamine **28** (0.524 g, 57%): mp 147-148 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.53-3.50 (m, 6 H, $-CH_2-$), 3.68 (s, 3 H, CH_3O), 4.23 (t, J = 6.5 Hz, 1 H, ArCHN), 5.07 (s, 2 H, $PhCH_2O$), 5.85 (s, 2 H, OCH_2O), 6.45 (s, 1 H, ArH), 6.58 (s, 1 H, ArH), 6.67 (s, 3 H, ArH), 7.23-7.62 (m, 6 H, ArH and OH). Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.36; H, 5.98; N, 3.27.

1-(2-Pyridylmethyl)-1,2,3,4-tetrahydroisoquinoline (29). A mixture of hydroxylamine **26** (0.240 g, 1.00 mmol), 5% palladium on charcoal (0.076 g), and acetic acid (20 mL) was vigorously stirred under H_2 for 60 h. The catalyst was separated by filtration through Celite, and the filtrate was evaporated. A hydrochloric acid (1 N, 10 mL) was added to the residue, and the solution was washed with ether (5 mL). The aqueous layer was basified with an 8 N aqueous sodium hydroxide and extracted with dichloromethane (5 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to give amine **29** (0.185 g, 83%): IR (neat) 3300, 3020, 2930, 2840, 1600, 1570, 1500, 1480, 1460, 1440, 1380, 1320, 1120, 1000, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.07-2.40 (br, 1 H, NH), 2.60-3.60 (m, 6 H, $-CH_2-$), 4.33-4.73 (m, 1 H, ArCHN), 6.93-7.76 (m, 7 H, ArH), 8.53 (d, J = 4.0 Hz, 1 H, CH=N—).

2-Phenylpyrrolidine (31). To a mixture of hydroxylamine **23** (0.163 g, 1.00 mmol), water (5.8 mL), and HCl (1.4 mL) was added zinc powder (0.468 g, 7.16 mmol), and the mixture was stirred at 100 °C for 2 h. The mixture was made basic with 30% aqueous sodium hydroxide and extracted with ether (15 mL × 5). The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to afford cyclic amine **31**[63] (0.123 g, 84%) as a colorless liquid.

3-(1-Methyl-2-pyrrolidinyl)pyridine (Nicotine) (32). Catalytic hydrogenation of **24** over palladium on charcoal in acetic acid under H_2 gave **30**[63] in 70% yield. To a solution of **30**, aqueous formaldehyde, and sodium cyanoborohydride in acetonitrile was added acetic acid dropwise until the solution becomes neutral. The usual treatment gave **32**[45] in 91% yield.

1-Methyl-10-oxa-9-azatricyclo[3.3.1.1^{3,9}]decane (34). A mixture of hydroxylamine **25** (0.311 g, 2.0 mmol) and Pd black (0.043 g, 0.4 mmol) in toluene (5 mL) was stirred for 40 h at reflux temperature. To the mixture was added ether (10 mL), and the mixture was filtered through Celite. The filtrate was evaporated, and Kugelrohr distillation gave isoxazolidine **34** (0.171 g, 56%): bp 77-86 °C (4 mmHg) (Kugelrohr); IR (neat) 2975, 2940, 2880, 1480, 1455, 1290 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.20 (s, 3 H, CH_3), 1.33-2.34 (m, 10 H, $-CH_2-$), 3.40-3.83 (m, 1 H, —CHN—), 4.80 (t, J = 5.0 Hz, 1 H, —CHO—).

Registry No. **1**, 86544-58-3; **2**, 94143-77-8; **3**, 3376-26-9; **4**, 3376-24-7; **5**, 24423-87-8; **6**, 98809-70-2; **7**, 94143-78-9; **8**, 24423-88-9; **9**, 113123-23-2; **10**, 34418-91-2; **11**, 55386-67-9; **12**, 4781-58-2; **13**, 16249-34-6; **14**, 94617-77-3; **15**, 94143-79-0; **16**, 94143-80-3; **17**, 94617-79-5; **18**, 94617-80-8; **22**, 102564-44-3; **23**, 99075-08-8; **24**, 125198-33-6; **25**, 94143-81-4; **26**, 75997-56-7; **27**, 125198-34-7; **28**, 125198-35-8; **29**, 125198-36-9; **30**, 13450-58-3; **31**, 1006-64-0; **32**, 75202-10-7; **34**, 94143-82-5; CH_3MgI, 917-64-6; PhBr, 108-86-1; $HNBu_2$, 111-92-2; $HN(Pr\text{-}i)_2$, 108-18-9; $PhCH_2NHCH_2Ph$, 103-49-1; $PhCH_2NHBu\text{-}t$, 3378-72-1; $PhCH_2NHMe$, 103-67-3; PhCH=N(=O)Me, 3376-23-6; H_2C=CHOBu, 111-34-2; H_2C=$CHCH_2BrMg$, 1730-25-2; 3-bromopyridine, 626-55-1; 1,2,3,4-tetrahyrdoisoquinoline, 91-21-4; 6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline, 98809-69-9; 6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline, 94143-83-6; pyrrolidine, 123-75-1; methyl 2-pyrrolidinecarboxylate, 2577-48-2; piperidine, 110-89-4; 2-methylpiperidine, 109-05-7; benzaldoxime, 932-90-1; morpholine, 110-91-8; 2,3-(methylenedioxy)benzyl bromide, 101417-40-7; 2-picoline, 109-06-8.

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Tungstate-Catalyzed Oxidation of Tetrahydroquinolines with Hydrogen Peroxide: A Novel Method for the Synthesis of Cyclic Hydroxamic Acids

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The sodium tungstate catalyzed oxidation of 1,2,3,4-tetrahydroquinolines (**1**) with 30% aqueous hydrogen peroxide solution in methanol gives 1-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones (**2**), which are important biologically active compounds, in good to excellent yields. The cyclic hydroxamic acid **7** is also obtained in good yield. Since reduction of **2** thus obtained gives 3,4-dihydroquinolin-2(1*H*)-ones (**4**), the present reaction provides a convenient method for synthesis of **4** from **1**.

Flavin monooxygenase[1] and model compounds, such as 5-ethyl-4a-hydroperoxyisoalloxazines[2,3] effect oxidation of secondary amines to give nitrones. Simulation of this function with transition metal complex catalysts led the

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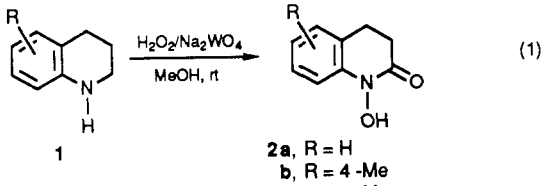
discovery of the catalytic oxidation of secondary amines with hydrogen peroxide in the presence of sodium tungstate[4] or selenium dioxide[5] to give the corresponding nitrones. During the course of study on the catalytic oxidation of secondary amines a novel method for the synthesis of cyclic hydroxamic acids has been explored.[6] Thus, treatment of 1,2,3,4-tetrahydroquinolines (1) with 30% aqueous hydrogen peroxide in the presence of tungstate catalyst gave 1-hydroxy-3,4-dihydroquinolin-2-(1*H*)-ones (**2**), which have potent antibacterial activity,[7] in excellent yields as depicted in eq 1.



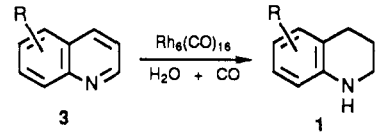
(1)

1

2a, R = H
b, R = 4-Me
c, R = 6-Me
d, R = 6-MeO
e, R = 6-MeCONH
f, R = 6-Cl
g, R = 6-Br
h, R = 6-MeCO
i, R = 6-CN
j, R = 8-Me

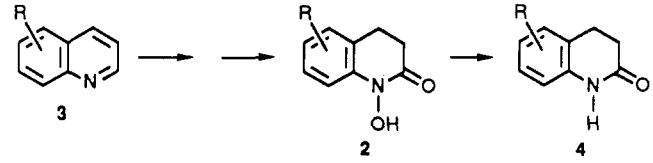
Hydroxamic acids are important biologically active compounds,[8] such as antibiotic antagonists,[8a] tumor inhibitors,[8a] cell-division factors,[8a] potent growth factors,[8b] antibiotics,[8c] or microbial iron transport compounds.[8d,e] Although the synthetic methods for aliphatic hydroxamic acids are well documented,[9] the methods for the synthesis of cyclic hydroxamic acids are limited to few reactions, which involve reductive cyclization of (*o*-nitrophenyl)-propionic esters[7a,10] or acids[7b,c,11] and oxidation of trimethylsilylated amides.[9d,e]

We recently found that rhodium cluster catalyzed hydrogenation of quinolines (**3**), which are easily obtained from coal and oil shale, under water–gas shift reaction conditions gives 1,2,3,4-tetrahydroquinolines **1** selectively in high yields;[12] therefore, the present reaction provides a highly useful method for the synthesis of hydroxamic acids **2** from quinolines **3**. Furthermore, reduction of



3 1

hydroxamic acids **2** gives 3,4-dihydroquinolin-2(1*H*)-ones (**4**),[11c] which have potent physiological activities such as β-adrenergic blocking action.[13]



3 2 4

Results and Discussion

The treatment of 1,2,3,4-tetrahydroquinoline (**1a**) with 3 molar equiv of 30% aqueous hydrogen peroxide in methanol in the presence of metal catalyst gave 1-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**2a**) along with small amounts of quinoline (**3a**). $Na_2WO_4 \cdot 2H_2O$ was found to be the most effective catalyst, and other catalysts such as H_2WO_4, Na_2MoO_4, $MoO_2(acac)_2$, $VO(acac)_2$, and CeO_2 gave poor yields of hydroxamic acids. The oxidation of **1a** by using a catalyst such as CuCl, $CuCl_2$, $RuCl_2(PPh_3)_3$, $Fe(acac)_2$, and $Mo(CO)_6$ gave quinoline in 30–40% yields. When **1a** was oxidized with a catalyst such as CuO, CuCl, and $CuCl_2$, 1-formyl-1,2,3,4-tetrahydroquinoline (**5a**) was obtained in low yield. The copper-catalyzed oxidation of methanol would give formic acid which undergoes condensation with **1a** to give **5a**.

The oxidation reaction is strongly affected by the solvent used. Water gave the best yield of **2a**, which precipitated out. The best result has been obtained with 0.1 M concentration of amines. When the concentration of amines is higher than 0.5 M, the reaction gave tarlike products. The rate of addition of hydrogen peroxide is not related to the yields of hydroxamic acids. When the reaction was carried out at 35 °C, the yields of hydroxamic acids become lower in comparison with the reaction at room temperature. For the oxidation of water-insoluble substrates such as 6-methyl-, 6-methoxy-, and 6-acetyl-1,2,3,4-tetrahydroquinolines, methanol gave better results in comparison with water. The oxidation did not proceed in dichloromethane, tetrahydrofuran, and dioxane because of low solubility of the catalyst.

Generally, 1,2,3,4-tetrahydroquinolines can be converted into the corresponding hydroxamic acids highly efficiently upon treatment with 3 molar equiv of hydrogen peroxide in the presence of 1–3 mol % of $Na_2WO_4 \cdot 2H_2O$ at room temperature in a single step. The typical results of the preparation of hydroxamic acids are summarized in Table

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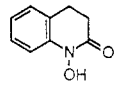
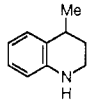
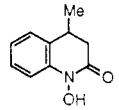
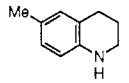
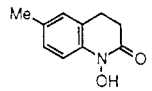
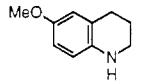
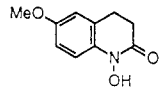
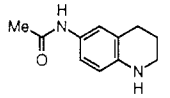
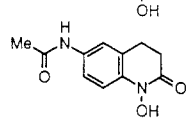
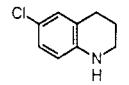
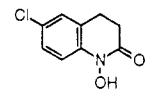
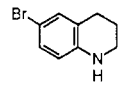
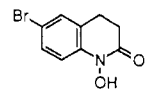
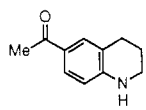
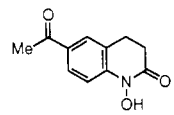
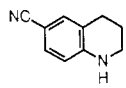
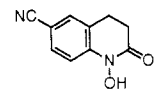
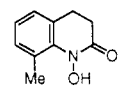
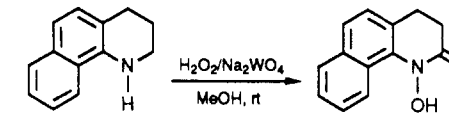
Table I. Tungstate-Catalyzed Oxidation of 1,2,3,4-Tetrahydroquinoline Derivatives with Hydrogen Peroxide[a]

entry	amine	product[b]	isolated yield, %
1	 1a	 2a	84
2	 1b	 2b	83
3	 1c	 2c	82
4	 1d	 2d	83
5	 1e	 2e	85
6	 1f	 2f	58
7	 1g	 2g	59
8	 1h	 2h	52
9	 1i	 2i	57
10	 1j	 2j	57

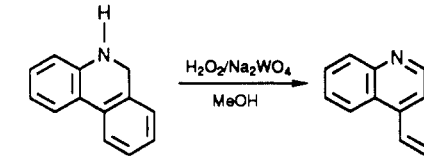
[a] Reaction was carried out by using amine (0.1 M), Na_2WO_4 (2 mol %), H_2O_2 (3 molar equiv) in methanol at room temperature under argon. [b] Products gave satisfactory IR, NMR, and elementary analytical data.

I. It is important that the acetamido derivative **2e** was obtained in high yield, since the acetamido group can be transformed into various functional groups. The acetyl group at C-6 and methyl group at C-8 decrease the yields of the hydroxamic acids, indicating that the oxidation is influenced by electric and steric effects. The oxidation of 1,2,3,4-tetrahydrobenzoquinoline (**6**) gave the corresponding hydroxamic acid **7** in 55% yields.

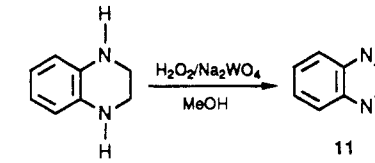


6 **7** (55%)

Although small amounts of quinolines have been detected as byproducts, in some cases aromatized products become the main products. Thus, oxidations of 1,2,3,4-tetrahydro-2-methylquinoline (**1k**), 5,6-dihydrophenanthridine (**8**), and 1,2,3,4-tetrahydroquinoxaline (**10**) under the same reaction conditions gave 2-methylquinoline (**3k**, 48%), phenanthridine (**9**, 81%) and quinoxaline (**11**, 37%), respectively.



8 **9**



10 **11**

When substrates are soluble in neither water nor methanol, the phase-transfer catalytic system can be used. The activity of various phase-transfer catalysts has been examined for the oxidation of **1a** with aqueous hydrogen peroxide in water–CH_2Cl_2 (Table II). Methyltrioctylammonium chloride (Aliquat 336) is the most effective phase-transfer catalyst; hexadecyltrimethylammonium chloride gave a good yield of **2a**; other catalysts such as tetramethylammonium iodide, tetramethylammonium bromide, tetraethylammonium iodide, benzyltrimethylammonium chloride, and benzyltrimethylammonium hydroxide gave poor yields of **2a**. The treatment of **1a** with hydrogen peroxide in the presence of $Na_2WO_4 \cdot 2H_2O$ and Aliquat 336 in water or a nonpolar solvent such as dichloromethane, chloroform, ether, benzene, and hexane gave **2a** within 1–2 h in 61–68% yield. The rate of the oxidation of **1a** under phase-transfer reaction conditions was 10 times faster than that under homogeneous conditions.

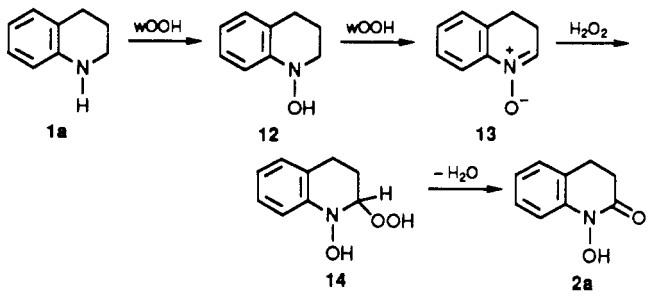
The present catalytic reaction can be rationalized by assuming the mechanism depicted in Scheme I. The oxidation of **1a** with tungstate peracid (wOOH) (w = WO_3^-, WO_4^-, WO_6^-), which is formed from tungstate and hydrogen peroxide,[14] gives hydroxylamine **12**. Further oxi-

Table II. Effect of Phase-Transfer Catalyst for the Oxidation of Amine 1a under Phase-Transfer-Catalytic Reaction Conditions[a]

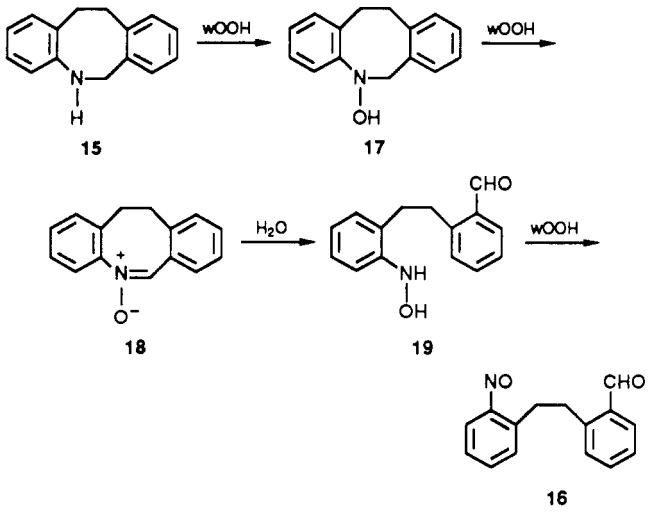
	ammonium salt						
entry	compd	mol %	Na_2WO_4, mol %	solvent	time, h	convn,[b] %	yield[b,c] **2a**, %
1	none	0	5	CH_2Cl_2	1.0	40	68
2	Aliquat 336	5	5	CH_2Cl_2	1.0	94	76
3	$C_{16}H_{33}NMe_3Cl$	5	5	CH_2Cl_2	1.0	97	63
4	$PhCH_2NEt_3Cl$	5	5	CH_2Cl_2	1.0	44	41
5	$PhCH_2NMe_3Cl$	5	5	CH_2Cl_2	1.0	23	69
6	Me_4NI	5	5	CH_2Cl_2	1.0	1	–
7	Me_4NBr	5	5	CH_2Cl_2	1.0	8	34
8	Et_4NI	5	5	CH_2Cl_2	1.0	5	–
9	$PhCH_2NMe_3(OH)$	5	5	CH_2Cl_2	1.0	58	35

[a] Reaction was carried out using amine **1a** (3 mmol), 30% aqueous H_2O_2 (18 mmol), sodium tungstate, and ammonium salt at room temperature under argon. [b] Determined by GLC. [c] Based on converted amine **1a**.

Scheme I



Scheme II



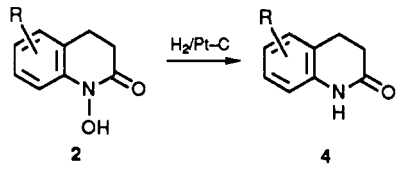
dation of **12** gives nitrone **13**,[4] which undergoes electrophilic reaction with H_2O_2 to give **14**. Dehydration of **14** would give hydroxamic acid **2a**. It is noteworthy that the reaction of nitrones with *m*-chloroperbenzoic acid gives hydroxamic acids.[15]

The oxidation of 5,6,11,12-tetrahydrodibenz[*b,f*]azocine (**15**) under the same reaction conditions gave 2-[2-(2-nitrosophenyl)ethyl]benzaldehyde (**16**) in 31% yield. Initially formed *N*-hydroxylamine **17** gives 11,12-dihydrodibenz[*b,f*]azocine *N*-oxide (**18**), which is hydrolyzed under the reaction condition to give hydroxylamino aldehyde **19**. Oxidation of **19** would give **16** (Scheme II).

The oxidation of 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine (**20**) gave hydroxamic acid **2a** in 44% yield. The reaction involves peculiar ring contraction. The formation of **2a** from **20** can be rationalized by assuming the following mechanism. Amine **20** is oxidized to give hydroxamic acid. Lossen type rearrangement[16] of hydroxamic acid mediated by tungstate would give carbon dioxide and 1,2,3,4-tetrahydroquinoline (**1a**), which undergoes similar oxidation to give **2a**.

The reduction of hydroxamic acids gives 3,4-dihydroquinolin-2(1*H*)-ones,[11c] which have been prepared by Friedel-Craft's alkylation[17] of *N*-(3-chloropropionyl)anilines or hydrogenation[18] of carbostyrils.

In summary, the tungstate-catalyzed oxidation of 1,2,3,4-tetrahydroquinolines with hydrogen peroxide gives



1-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones highly efficiently.

Experimental Section

General. ^1H NMR spectra were measured on JEOL Model JNM PMX-60SI (60 MHz) and JNM GSX-270 (270 MHz) spectrometers; IR spectra were recorded on a Hitachi Model 215 spectrometer and a Shimadzu Model FTIR-4100 spectrometer. GLC for analysis was carried out on Shimadzu Model GC-8A flame ionization gas chromatography by using a 1 m × 4 mm, 10% SE-30 on Uniport HP under the conditions of injection temperature (200 °C), column temperature (100–250 °C), and nitrogen gas pressure (0.5 kg/cm^2). Elemental analyses were carried out on a Yanagimoto MT-2 CHN corder. Mass spectra were measured on a Hitachi RSM-4 mass spectrometer, and exact mass spectra were measured on a JEOL JMS-DX-303 mass spectrometer. Thin-layer chromatography (0.2 mm) was carried out with silica gel 60 PF254 (Merck). GLC for purification was carried out on a JEOL Model JGC-20KT thermal conductive chromatograph by using a 2 m × 4 mm, 10% SE-30 under the conditions of injection temperature (200 °C) and detector temperature (200 °C).

Materials. 1,2,3,4-Tetrahydroquinolines **1b–d,f,j,k** were prepared by the $Rh_6(CO)_{16}$-catalyzed hydrogenation of the corresponding quinolines under water–gas shift reaction conditions by the known method.[12] Amine **1g** was prepared by the bromination of amine **1a**.[19] Amine **1h** was prepared by the Friedel–Craft's acylation[20] of amine **1a**. Amino **1i** was prepared by cyanation of amine **1g** with cuprous cyanide in dimethylformamide.[21] Amine **1e** was prepared by the Schmidt reaction[22] of amine **1h** with hydrogen azide.[23] 1,2,3,4-Tetrahydro-7,8-benzoquinoline (**6**) and 5,6-dihydrophenanthridine (**8**) were prepared by the hydrogenation of 7,8-benzoquinoline and phenanthridine (**9**), respectively, by using $Rh_6(CO)_{16}$ catalyst in methanol. 1,2,3,4-Tetrahydroquinoxaline (**10**)[24] and 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine (**20**)[22,25] were prepared by the known methods. Secondary amines and 1-tetralone were distilled or recrystallized prior to use. Solvents, catalysts, and ammonium salts were commercially available and used without further purification, except $Mo(CO)_6$ which was sublimated at 60 °C (4 mmHg) before use.

Effect of Catalysts and Solvents for the Oxidation of 1,2,3,4-Tetrahydroquinoline (1a). To a mixture of amine **1a** (133 mg, 1.00 mmol) and a catalyst (2 mol %) in methanol (10 mL) was added dropwise 30% aqueous hydrogen peroxide (340 mg, 3.10 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 24 h. The products were 1-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**2a**), quinoline (**3a**), and 1-formyl-1,2,3,4-tetrahydroquinoline (**5a**) which were identified by comparison with their authentic samples (see below). The yields were determined by GLC analysis using an internal standard (*n*-eicosane). The results are as follows: $Na_2WO_4{\cdot}2H_2O$ conversion 100%, yield of **2a**, 89%, **3a**, 3%; H_2WO_4, 93, 9, 14; SeO_2, 72, 22, 5; $Na_2MoO_4{\cdot}2H_2O$, 79, 28, 9; $Mo(CO)_6$, 89, 11, 30; $MoO_2(acac)_2$, 79, 11, 23; $H_2MoO_4{\cdot}H_2O$, 64, 9, 21; $RuCl_2(PPh_3)_3$, 100, 6, 33; $RuCl_2(PPh_3)_4$, 91, 4, 30; $Ti(O^iPr)_4$, 100, 18, 12; CuO, 48, 0, 1, (**5a**, 8%); CuCl, 92, 0, 31, (10); $CuCl_2$, 92, 0, 23, (8); $Fe(acac)_2$, 84, 19,

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41; V_2O_5, 75, 9, 12; $VO(acac)_2$, 42, 5, 13; $NaVO_3$, 18, 6, 31. The oxidation does not proceed in the presence of a catalyst such as WO_3 and MoO_3 because of low solubility in methanol. The solvent effect was determined similarly by using sodium tungstate catalyst (2 mol %) for 12 h. The results are as follows: water conversion 90%, yield 99%; methanol 90, 90; ethanol 72, 67; nitromethane 89, 51; dichloromethane 8, 0.

General Procedure for the Catalytic Oxidation under Phase-Transfer Reaction Conditions. To a solution of amine **1a** (400 mg, 3.00 mmol) and ammonium salt (0.15 mmol) in a solvent (3 mL) was added a solution of 30% aqueous hydrogen peroxide (1.8 mL, 18 mmol) and sodium tungstate (50 mg, 0.15 mmol) in water (0.1 mL) at room temperature under argon. The reaction mixture was stirred at room temperature. GLC analysis was carried out similar to above manner. The results are summarized in Table II. The oxidation of **1a** under phase-transfer reaction conditions (90% conversion after 45 min) proceeds faster than that under homogeneous conditions (90% conversion after 12 h).

The Sodium Tungstate Catalyzed Oxidation of 1,2,3,4-Tetrahydroquinolines with Hydrogen Peroxide: General Procedure. To a mixture of amine **1a** (353 mg, 2.65 mmol) and sodium tungstate (17 mg, 0.05 mmol) in methanol (25 mL) was added dropwise 30% aqueous hydrogen peroxide (0.81 mL, 7.9 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 24 h. After removal of methanol under reduced pressure, the residue was extracted with CH_2Cl_2 (20 mL × 5). The extracts were dried over $MgSO_4$ and evaporated. Column chromatography (SiO_2, 20 mm × 80 mm, hexane–CH_2Cl_2) gave 1-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**2a**) (356 mg, 82% yield): mp 117–118 °C (pentane–CH_2Cl_2); R_f 0.36 (SiO_2, ether); IR (Nujol) 3000–2700 (O—H), 1690 (C=O), 1605 (C—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78 (t, J = 6.0 Hz, 2 H, $COCH_2CH_2$), 2.83 (t, J = 6.0 Hz, 2 H, $ArCH_2CH_2$), 6.82–7.58 (m, 4 H, Ar*H*), 8.35–9.58 (br s, 1 H, O*H*); mass spectra m/e 163 (M^+), 147 (M − 16), 146 (M − 17), 128, 117, 108. Anal. Calcd for $C_8H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.08; H, 5.43; N, 8.48.

1-Hydroxy-4-methyl-3,4-dihydroquinolin-2(1*H*)-one (2b): 83% yield; mp 79–80.5 °C (hexane–CH_2Cl_2); R_f 0.44 (SiO_2, ether); IR (Nujol) 3200–2700 (O—H), 1650 (C=O), 1605 (C—C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 7.0 Hz, 3 H, CH_3), 2.70 (d, J = 7.5 Hz, 2 H, $COCH_2CH$), 2.73 (tq, J = 7.5, 15.0 Hz, 1 H, CH_2CHCH_3), 6.93–7.70 (m, 4 H, Ar*H*), 9.6–10.1 (br s, 1 H, O*H*); mass spectra m/e 177 (M^+), 132, 118. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.89; H, 6.25; N, 7.88.

1-Hydroxy-6-methyl-3,4-dihydroquinolin-2(1*H*)-one (2c): 82% yield; mp 137.8–138.5 °C (hexane–CH_2Cl_2); R_f 0.35 (SiO_2, ether); IR (Nujol) 3150–2750 (O—H), 1645 (C=O), 1285, 1245, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3 H, CH_3), 2.73 (t, J = 5.0 Hz, 2 H, $COCH_2CH_2$), 2.76 (t, J = 5.0 Hz, 2 H, $ArCH_2CH_2$), 6.84 (s, 1 H, Ar*H* on C-5), 7.10 (d, J = 8.0 Hz, 1 H, Ar*H* on C-7), 7.16 (d, J = 8.0 Hz, 1 H, Ar*H* on C-8), 8.0–10.0 (br s, 1 H, O*H*). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.88; H, 6.22; N, 7.83.

1-Hydroxy-6-methoxy-3,4-dihydroquinolin-2(1*H*)-one (2d): 83% yield; mp 141.5–141.8 °C (hexane–CH_2Cl_2); R_f 0.24 (SiO_2, ether); IR (Nujol) 2720 (O—H), 1690 (C=O), 1500 (C—C), 1315, 1250, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (t, J = 5.6 Hz, 2 H, $COCH_2CH_2$), 2.80 (t, J = 5.6 Hz, 2 H, $ArCH_2CH_2$), 3.74 (s, 1 H, CH_3O), 6.63 (s, 1 H, Ar*H* on C-5), 6.70 (dd, J = 8.0, 2.2 Hz, 1 H, Ar*H* on C-7), 7.26 (d, J = 8.0 Hz, 1 H, Ar*H* on C-8), 8.7–10.5 (br s, 1 H, O*H*). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.10; H, 5.66; N, 7.22.

6-Acetamido-1-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (2e): 85% yield; mp 140–141 °C (EtOH); R_f 0.16 (SiO_2, $CHCl_3$–MeOH, 10:1); IR (Nujol) 3200–2700 (O—H), 1650 (C=O), 1600 (C—C), 1550, 1270, 1200 cm^{-1}; ^1H NMR (CD_3OD) δ 2.13 (s, 3 H, CH_3), 2.77 (t, J = 7.1 Hz, 2 H, $COCH_2CH_2$), 2.82 (t, J = 7.1 Hz, 2 H, $ArCH_2CH_2$), 7.13–7.70 (m, 3 H, Ar*H*), 8.47 (br s, 1 H, N*H*); mass spectra m/e (rel %) 220 (M^+, 100), 204 (26), 178 (24), 162 (33), 161 (64), 133 (44); exact mass calcd for $C_{11}H_{12}N_2O_3$ 220.0848, found 220.0857.

6-Chloro-1-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (2f): 58% yield; mp 145.5–148.0 °C (hexane–CH_2Cl_2); R_f 0.24 (SiO_2, ether); IR (Nujol) 2700 (O—H), 1675 (C=O), 1485, 1430, 1285 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81 (t, J = 5.0 Hz, 2 H, $COCH_2CH_2$), 2.84 (t, J = 5.0 Hz, 2 H, $ArCH_2CH_2$), 7.00–7.50 (m, 3 H, Ar*H*), 9.2 (br s, 1 H, O*H*). Anal. Calcd for $C_9H_8NO_2Cl$: C, 54.70; H, 4.80; N, 7.09; Cl, 17.94. Found: C, 54.55; H, 4.06; N, 7.08; Cl, 18.04.

6-Chloroquinoline (3f) (5 mg, 5% yield): R_f 0.45 (SiO_2, ether); IR Nujol) 1590 (C—C), 1490, 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.87 (m, 4 H, Ar*H*), 7.95 (s, 1 H, Ar*H* on C-5), 8.09 (s, 1 H, Ar*H* on C-4), 8.85 (dd, 1 H, Ar*H* on C-2).

6-Bromo-1-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (2g): 59% yield; mp 128–128.5 °C (hexane–CH_2Cl_2); R_f 0.32 (SiO_2, ether); IR (Nujol) 1687 (C=O), 1674, 1635, 1597 (C—C), 1516, 1282, 1219, 1192, 819 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.75 (t, J = 7.5 Hz, 2 H, $COCH_2CH_2$), 2.93 (t, J = 7.5 Hz, 2 H, $ArCH_2CH_2$), 7.22 (d, J = 8.5 Hz, 2 H, Ar*H* on C-8), 7.29 (s, 1 H, Ar*H* on C-5), 7.41 (dd, J = 8.5, 2.2 Hz, 1 H, Ar*H* on C-7), 9.06 (br s, 1 H, O*H*); mass spectra m/e (rel %) 243 (M^+ + 2, 80), 241 (M^+, 82), 227 (26), 225 (29), 173 (12), 171 (16), 117 (100); exact mass calcd for $C_9H_8NO_2{}^{79}Br$ 240.9739, found 240.9703; calcd for $C_9H_8NO_2{}^{81}Br$ 242.9718, found 242.9723. Anal. Calcd for $C_9H_8NO_2Br$: C, 44.65; H, 3.33; N, 5.79; Br, 33.01. Found: 44.68; H, 3.33; N, 5.77; Br, 33.16.

6-Acetyl-1-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (2h): 52% yield; mp 163–164 °C (CH_2Cl_2); R_f 0.20 (SiO_2, ether); IR (Nujol) 3200–2700 (O—H), 1660 (C=O), 1605 (C—C), 1520, 1435, 1360, 1340, 1290 1265, 1210, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.57 (s, 3 H, CH_3), 2.87 (t, J = 7.1 Hz, 2 H, $COCH_2CH_2$), 2.93 (t, J = 7.1 Hz, 2 H, $ArCH_2CH_2$), 7.38 (d, J = 8.6 Hz, 1 H, Ar*H* on C-8), 7.75 (d, J = 2.5 Hz, 1 H, Ar*H* on C-5), 7.82 (dd, J = 8.6, 2.5 Hz, 1 H, Ar*H* on C-7), 8.2–9.9 (br s, 1 H, O*H*). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.25; H, 5.38; N, 6.82.

Column chromatography (SiO_2, 20 × 70 mm, CH_2Cl_2) gave 6-acetylquinoline (**3h**) (19% yield) which was further purified by Kugelrohr distillation (87 mg, 14% yield): bp 190–200 °C (6 mmHg) (Kugelrohr); mp 77.0–77.5 °C (hexane–CH_2Cl_2); R_f 0.35 (SiO_2, ether); IR (Nujol) 1680 (C=O), 1625, 1600, 1580, 1500 (C—C), 1370, 1325, 1280, 1255, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (s, 3 H, CH_3CO), 7.40 (dd, J = 8.0, 4.0 Hz, 1 H, Ar*H* on C-3), 8.10–8.50 (m, 4 H, Ar*H* on C-4,5,7,8), 8.93 (dd, J = 4.0, 2.0 Hz, 1 H, Ar*H* on C- 2). Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.98; H, 5.23; N, 8.12.

6-Cyano-1-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (2i): 57% yield; mp 209–210 °C (MeOH); R_f 0.75 (SiO_2, MeOH–CH_2Cl_2, 1:4); IR (Nujol) 3060 (O—H), 2226 (CN), 1670 (C=O), 1637, 1607 (C—C), 1495, 1365, 827 cm^{-1}; ^1H NMR (CD_3OD) δ 2.73 (t, J = 7.0 Hz, 2 H, $COCH_2CH_2$), 2.99 (t, J = 7.5 Hz, 2 H, $ArCH_2CH_2$), 7.45 (d, J = 8.3 Hz, 1 H, Ar*H* on C-8), 7.56 (s, 1 H, Ar*H* on C-5), 7.64 (dd, J = 8.3, 1.8 Hz, 1 H, Ar*H* on C-7). Anal. Calcd for $C^{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.92; H, 4.39; N, 14.92.

1-Hydroxy-8-methyl-3,4-dihydroquinolin-2(1*H*)-one (2j): 57% yield; mp 113–114 °C (hexane–CH_2Cl_2); R_f 0.48 (SiO_2, ether); IR (Nujol) 3250–2700 (O—H), 1660 (C=O), 1600 (C—C), 1260, 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (s, 3 H, CH_3), 2.74 (t, J = 5.0 Hz, 2 H, $COCH_2CH_2$), 2.78 (t, J = 5.0 Hz, 2 H, $ArCH_2CH_2$), 6.80–7.16 (m, 3 H, Ar*H*), 8.8–10.0 (br s, 1 H, O*H*); mass spectra m/e 177 (M^+), 161 (M − 16), 160 (M − OH), 132, 117, 96, 93, 81. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.78; H, 6.23; N, 7.89.

1-Hydroxy-3,4-dihydro-7,8-benzoquinolin-2(1*H*)-one (7): 55% yield; mp 145–149 °C (with decomp); R_f 0.42 (SiO_2, ether); IR (Nujol) 3200–3000 (O—H), 1669 (C=O), 1391, 1277, 1192, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.86 (t, J = 7.5 Hz, 2 H, CH_2CH_2CO), 3.09 (t, J = 7.5 Hz, 2 H, $ArCH_2CH_2$), 7.27 (d, J = 8.3 Hz, 1 H, Ar*H* on C-5), 7.45–7.55 (m, 2 H, Ar*H* on C-8,9), 7.63 (d, J = 8.3 Hz, 1 H, Ar*H* on C-6), 7.81 (dd, J = 2.4 and 7.7 Hz, 1 H, Ar*H* on C-7), 8.78 (dd, J = 1.7 and 8.1 Hz, 1 H, Ar*H* on C-10), 9.21 (s, 1 H, O*H*); mass spectra m/e (rel %) 213 (M^+, 100), 197 (29), 168 (59); exact mass calcd for $C_{13}H_{11}NO_2$ 213.0790, found 213.0804.

Oxidation of 2-Methyl-1,2,3,4-tetrahydroquinoline (1k). To a mixture of amine **1k** (469 mg, 3.19 mmol) and sodium tungstate (21 mg, 0.06 mmol) in methanol (30 mL) was added dropwise 30% aqueous hydrogen peroxide (1.96 mL, 19 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 25 h. The usual workup and column chromatography (SiO_2, 20 mm × 80 mm, CH_2Cl_2) gave 2-methylquinoline (**3k**) (219 mg, 48% yield): bp 90–100 °C (6 mmHg) (Kugelrohr); R_f 0.31 (SiO_2, CH_2Cl_2); IR (neat) 3050 (C—H), 1605 (C—C), 1565,

1425, 1375, 1315, 1225 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.70 (s, 3 H, CH_3), 7.07–8.05 (m, 6 H, Ar*H*).

Oxidation of 5,6-Dihydrophenanthridine (8). To a mixture of amine **8** (77 mg, 0.43 mmol) and sodium tungstate (3 mg, 0.01 mmol) in methanol (5 mL) was added dropwise 30% aqueous hydrogen peroxide (149 mg, 1.4 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 48 h. The usual workup and column chromatography (SiO_2, 15 mm × 70 mm, CH_2Cl_2) gave phenanthridine (**9**) (62 mg, 81% yield): mp 106.5–107.5 °C; R_f 0.47 (SiO_2, ether); IR (Nujol) 1970, 1940, 1910, 1625, 1590, 1580, 1490, 1400, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.44–8.30 (m, 6 H, Ar*H* on C-2,3,4,7,8,9), 8.53 (d, J = 7.0 Hz, 2 H, Ar*H* on C-1,10), 9.22 (s, 1 H, Ar*H* on C-6). Anal. Calcd for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.82. Found: C, 86.92; H, 5.03; N, 7.68.

Oxidation of 1,2,3,4-Tetrahydroquinoxaline (10). To a mixture of **10** (213 mg, 1.59 mmol) and sodium tungstate (10 mg, 0.03 mmol) in methanol (16 mL) was added dropwise 30% aqueous hydrogen peroxide (368 mg, 3.36 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 24 h. The usual workup and Kugelrohr distillation (155 °C (10 mmHg)) gave quinoxaline (**11**) (76 mg, 37% yield): mp 37–39 °C; R_f 0.15 (SiO_2, ether); IR (Nujol) 1495 (C—C), 1415, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50–7.85 (m, 2 H, Ar*H* on C-6,7), 7.90–8.20 (m, 2 H, Ar*H* on C-5,8), 8.76 (s, 2 H, Ar*H* on C-2,3).

Oxidation of 5,6,11,12-Tetrahydrodibenz[*b*,*f*]azocine (15). To a mixture of **15** (258 mg, 1.23 mmol) and sodium tungstate (8 mg, 0.02 mmol) in methanol (12 mL) was added dropwise 30% aqueous hydrogen peroxide (426 mg, 3.88 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 28 h. The usual workup and column chromatography (SiO_2, 15 mm × 90 mm, hexane–CH_2Cl_2) gave 2-[2-(2-nitrosophenyl)-ethyl]benzaldehyde (**16**) (91 mg, 31% yield): mp 94.0–94.5 °C; IR (Nujol) 1695 (C=O), 1600 (C—C), 1530 (N=O monomer), 1320, 1310 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.63 (dt, J = 2.0, 8.0 Hz, 2 H, CH_2 ortho to CHO), 4.12 (dt, J = 2.0, 8.0 Hz, 2 H, CH_2 ortho to N=O), 6.17 (d, J = 8.0 Hz, 1 H, Ar*H* meta to N=O), 7.00–7.83 (m, 7 H, Ar*H*), 10.13 (s, 1 H, C*H*O).

Oxidation of 2,3,4,5-Tetrahydro-1*H*-benz[*b*]azepine (20). To a mixture of amine **20** (794 mg, 5.39 mmol) and sodium tungstate (35 mg, 0.11 mmol) in methanol (50 mL) was added dropwise 30% aqueous hydrogen peroxide (1.79 g, 16.3 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 50 h. The usual workup and column chromatography (SiO_2, 20 mm × 130 mm, hexane–dichloromethane) gave 1-hydrozy-3,4-dihydroquinolin-2(1*H*)-one (**2a**) (294 mg, 33% yield): R_f 0.30 (SiO_2, ether); mp 117.5–118.5 °C; IR (Nujol) 3000–2700 (O—H), 1690 (C=O), 1605 (C—C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.78 (t, J = 6.0 Hz, 2 H, $COCH_2CH_2$), 2.83 (t, J = 6.0 Hz, 2 H, $ArCH_2CH_2$), 6.82–7.58 (m, 4 H, Ar*H*), 8.55 (br s, 1 H, O*H*). Anal. Calcd for $C_8H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.11; H, 5.53; N, 8.30.

Formation of 1-Formyl-1,2,3,4-tetrahydroquinoline (5a). To a mixture of amine **1a** (500 mg, 3.75 mmol) and copper dichloride (10 mg, 0.07 mmol) in methanol (40 mL) was added dropwise 30% aqueous hydrogen peroxide (1.1 mL, 11 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 20 h. The usual workup and column chromatography (SiO_2, 10 g, hexane–dichloromethane, 4:1) gave two products, **5a** and **3a**. **5a** (161 mg, 26% yield), which was further purified by GLC (column temperature 140 °C) to give 50 mg (8% yield) of colorless oil: R_f 0.47 (SiO_2, ether); IR (neat) 2930 (C—H), 1650 (C=O), 1255, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.95 (tt, J = 6.0, 6.0 Hz, 2 H, $CH_2CH_2CH_2$), 2.81 (t, J = 6.0, 2 H, $ArCH_2CH_2$), 3.79 (t, J = 6.0 Hz, 2 H, CH_2CH_2NH), 6.99–7.30 (m, 4 H, Ar*H*), 8.72 (s, 1 H, C*H*O); mass spectra m/e (rel %) 162 (M^+ + 1, 9), 161 (M^+, 79), 133 (15), 132 (M^+ – CHO, 100), 130 (11), 118 (20), 117 (25), 77 (20). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.23; H, 6.90; N, 8.40. Quinoline (**3a**) (107 mg, 23% yield): R_f 0.47 (SiO_2, ether); ^{1}H NMR ($CDCl_3$) δ 7.26 (dd, J = 4.3, 8.3 Hz, 1 H, Ar*H* on C-3), 7.4–7.7 (m, 3 H, Ar*H* on C-5,6,7), 8.00 (dd, J = 8.3, 1.8 Hz, 1 H, Ar*H* on C-4), 8.81 (dd, J = 4.3, 1.8 Hz, 1 H, Ar*H* on C-2); mass spectra m/e (rel %) 130 (M^+ + 1, 11), 129 (M^+, 100), 128 (M^+ – 1, 19), 102 (M^+ – 27, 26).

Registry No. **1a**, 635-46-1; **1b**, 19343-78-3; **1c**, 91-61-2; **1d**, 120-15-0; **1e**, 114235-55-1; **1f**, 49716-18-9; **1g**, 22190-35-8; **1h**, 113961-88-9; **1i**, 50741-36-1; **1j**, 52601-70-4; **1k**, 1780-19-4; **2a**, 771-19-7; **2b**, 113961-89-0; **2c**, 113961-90-3; **2d**, 113961-91-4; **2e**, 114259-70-0; **2f**, 114259-71-1; **2g**, 125076-71-3; **2h**, 113961-92-5; **2i**, 125076-72-4; **2j**, 114259-72-2; **3a**, 91-22-5; **3f**, 612-57-7; **3h**, 73013-68-0; **3i**, 91-63-4; **5a**, 2739-16-4; **6**, 5223-80-3; **7**, 125108-26-1; **8**, 27799-79-7; **9**, 229-87-8; **10**, 3476-89-9; **11**, 91-19-0; **15**, 5697-88-1; **16**, 114235-54-0; **20**, 1701-57-1; Na_2WO_4, 13472-45-2; 7,8-benzoquinoline, 230-27-3.

Lipase-Catalyzed Resolution of Acyclic Amino Alcohol Precursors[1]

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Lipase-catalyzed resolution of acyclic 2-azido alcohols as precursors for amino alcohols was readily accomplished. Butanoates of racemic acyclic azidoalkanols were hydrolyzed by using commercially available lipases from *Candida cylindracea* and *Pseudomonas fluorescens*, respectively. Some representative examples of acyclic secondary 2-azido alcohols have been obtained with enantiomeric excess ranging from 24 to >98%.

Introduction

Enzymatic hydrolysis has recently been used for the optical resolution of several highly functionalized chiral molecules such as amino acids, lactones, diesters, and hydroxy acids.[2] Surprisingly, there are only few reports on the resolution of chiral amino alcohols, in spite of their importance both as chiral building blocks and as products of pharmaceutical interest.[3,4] They represent important structural features of natural products such as adrenaline, β-adrenergic receptor blockers, and local anesthetics.[5] In

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