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# Synthesis of 6-Substituted-3-Hydroxy-4(1*H*)-Pyridinones: Oxidation-Michael Addition of 3-Hydroxy-4(1*H*)-Pyridinones

Miao-Sheng Li, Lian-Quan Gu*, Zhi-Shu Huang, Shao-Hua Xiao and Lin Ma

Department of Chemistry, Zhongshan University, Guangzhou 510275, China

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***Abstract:*** 2-Alkyl-3-hydroxy-4(1*H*)-pyridinones can be oxidized by silver(I) oxide in alcoholic solution to give 2-alkoxy-2-alkyl-1,2dihydro-pyridine-3,4-diones, which can subsequently undergo a Michael addition with nucleophiles to give 6-substituted-2-alkyl-3-hydroxy-4(1*H*)-pyridinones. 

***Keywords:*** Pyridones; Quinones; Oxidation; Michael reactions.

## INTRODUCTION

3-Hydroxy-4(1*H*)-pyridinone derivatives are of medicinal interest as potential antitumor agents and bidentate chelators.[1-4] Driscoll et al.[2] have suggested a mechanism of antitumor activity for *ortho*-hydroxy-pyridinones similar to that in the catechol-*ortho*-quinone series, involving possible sulfhydryl reactivity, but the detailed mechanism has not been established. We have found that pure 2-ethyl-3-hydroxy-4(1*H*)-pyridinone does not affect on lactate dehydrogenase (LDH) activity, but their oxidation products show high inhibitory effects on LDH. The evidence indicates the covalent interaction of inhibitors and essential functional groups of LDH, with subsequent irreversible inhibition. Our mechanistic study indicates that 2-ethoxy-2-ethyl-1,2-dihydro-pyridine-3,4-dione is a reactive species that subsequently undergoes a Michael addition with a nucleophilic functional group, such as amino or thiol in the reactive domain of LDH, resulting in inactivation of the enzyme. We refer to this inhibitory mechanism as oxidation-Michael addition.

E-mail: cedc14@zsulink.zsu.edu.cn

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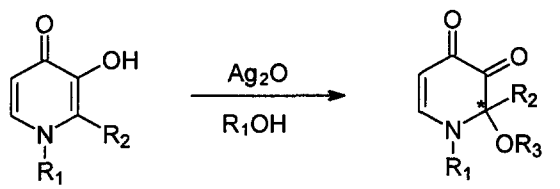
The oxidation-Michael addition not only explains the mechanism of biological function of *ortho*-hydroxypyridinone derivatives, but also can be used as a method to synthesize 6-substituted-3-hydroxy-4(1*H*)-pyridinones.

## RESULTS AND DISCUSSION

*Oxidation of 2-alkyl-3-hydroxy-4(1H)-pyridinones*

2-Alkyl-3-hydroxy-4(1*H*)-pyridinones **1** can be oxidized by the mild, one-electron oxidizing agent silver(I) oxide in an alcohol solution. It is interesting that the alcohol is involved in the reaction, and the resulting oxidation products are the 2-ethoxy-2-ethyl-1,2-dihydro-pyridine-3,4-dione **2** (scheme 1). This reaction appears not to have been reported before.




**1**

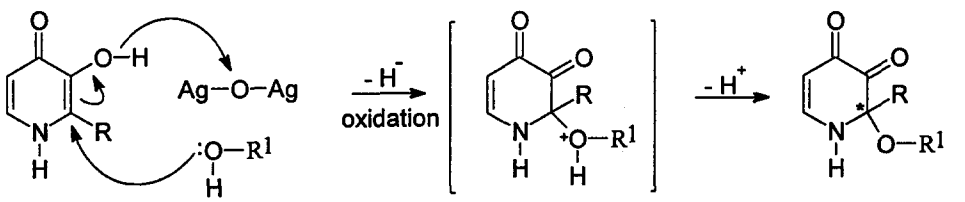
1a: $R_1 = H$, $R_2 = CH_3$
1b: $R_1 = H$, $R_2 = C_2H_5$
1c: $R_1 = CH_3$, $R_2 = CH_3$

**2**

2a: $R_1 = H$, $R_2 = CH_3$, $R_3 = C_2H_5$
2b: $R_1 = H$, $R_2 = C_2H_5$, $R_3 = CH_3$
2c: $R_1 = H$, $R_2 = C_2H_5$, $R_3 = C_2H_5$
2d: $R_1 = H$, $R_2 = C_2H_5$-, $R_3 = n$-$C_3H_7$
2e: $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$

**Scheme 1**

A possible reaction mechanism is shown in Scheme 2.




1 2

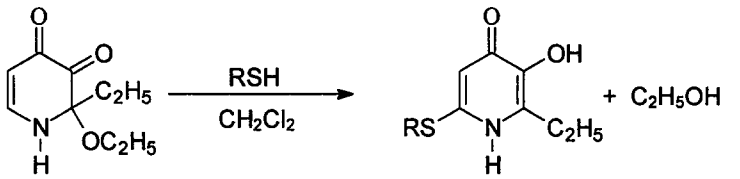
**Scheme 2**

$^1$H NMR analysis of the oxidation products indicates that all of the 2-alkoxy-2-alkyl-1,2-dihydro-pyridine-3,4-diones are the mixture of enantiomers with a ratio of 1 : 1.

Because the solvent alcohol is involved in the reaction, so the oxidation product structures depend on the alcohol used. Methanol, ethanol and *n*-propanol can be used as the reaction solvents.

*Dione reactions with thiols*

Compound **2c** undergoes Michael addition with thiols, such as 2-mercaptoethanol and thiophenol, and to give 6-substituted products (Scheme 3).



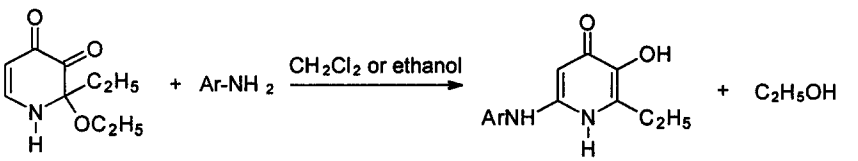

**2c** **3a**: R = $HOC_2H_4$
**3b**: R = Ph

**Scheme 3**

The yields of products are significantly affected by the solvents used. 2-ethoxy-2-ethyl-1,2-dihydro-pyridine-3,4-dione reacts with 2-mercaptoethanol or thiophenol in $CH_2Cl_2$ to give an almost quantitative yield of Michael addition product, but in aqueous solution large amounts of oxido-reductive products are formed.

*Dione reactions with anilines*

Compound **2c** undergoes Michael addition with anilines to give 6-substituted products (Scheme 4).



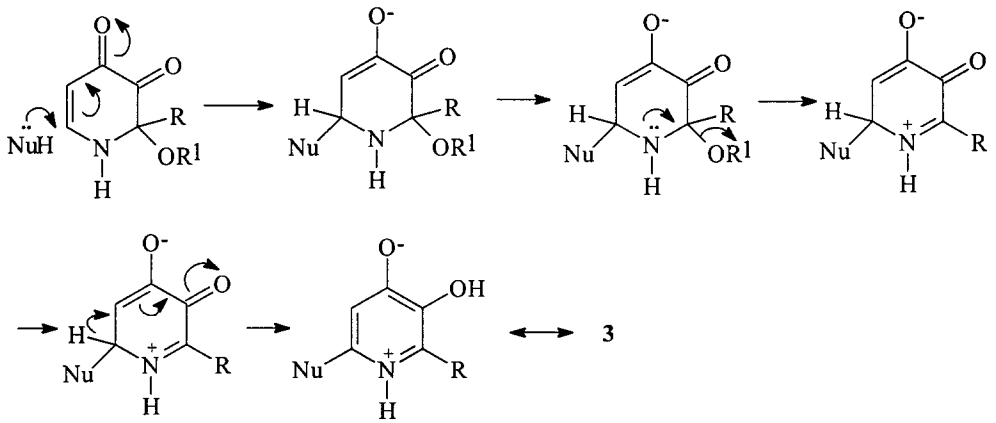

2c
4a: Ar = Ph
4b: Ar = *p*-$CH_3$-$C_6H_4$
4c: Ar = *p*-Br-$C_6H_4$

**Scheme 4**

*Oxidation-Michael addition of 3-hydroxy-4(1H)-pyridinone*

Most of the oxidation products **2** of 2-alkyl-3-hydroxy-4(1*H*)-pyridinones can be isolated and identified. The 2-alkoxy-2-alkyl-1,2-dihydro-pyridine-3,4-diones **2** are reactive species, that give Michael addition products with nucleophiles. It is convenient to synthesize the 6-substituted-2-alkyl-3-hydroxy--4(1*H*)-pyridinones **4** in a one-pot procedure from the pyridinones **1**.

The mechanism of reaction between 2-alkoxy-2-alkyl-1,2-dihydro-pyridine-3,4-diones and nucleophiles is shown in Scheme 5.



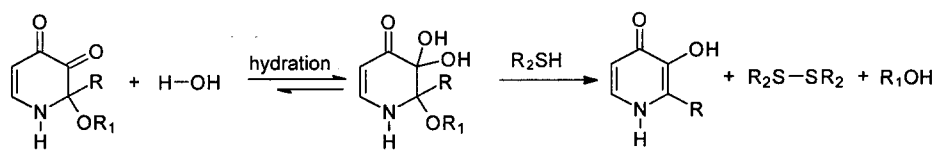

**Scheme 5**

The Michael addition intermediates are unstable, and aromatise to structures **3**.

*Competition between Michael addition and oxido-reduction*

Michael addition is a nucleophilic addition. An aprotic solvent enhances the nucleophilicity of a nucleophile.[6] 2-alkoxy-2-alkyl-1,2-dihydro-pyridine-3,4-diones react with thiols in aprotic solvent, such as $CH_2Cl_2$, resulting in high yields of Michael addition products. The major reaction between 2-alkoxy-2-alkyl-1,2-dihydro-pyridine-3,4-diones and thiols in aqueous solution is oxido-reduction, rather than a Michael addition.

2-alkoxy-2-alkyl-1,2-dihydro-pyridine-3,4-diones are stable in aprotic solvents. In aqueous solution, they undergo hydration to yield covalent hydrates. This phenomenon is somewhat similar to ninhydrin hydrate formation. The process of hydration has been monitored by UV spectroscopy. 2-Ethoxy-2-ethyl-1,2-dihydro-pyridine-3,4-dione **2c**, UV ($H_2O$): $\lambda_{max}$ (log ε): 377 (4.06) nm; 2-ethoxy-2-ethyl-2,3-dihydro-3,3-dihydroxypyridin-4(1*H*)-one, UV ($H_2O$): $\lambda_{max}$ (log ε): 307 (3.85) nm (Scheme 6).




**2** hydrate pyridine-dione **1**

**Scheme 6**

The pyridinedione hydrates are good oxidising regents, but inactive in the Michael additions, possibly because of loss of the *o*-quinone structural feature.

## EXPERIMENTAL PART

**General.** $^1$H NMR spectra were recorded in DMSO-$d_6$ solution on a Bruker AMX 400 MHz nmr spectrometer or a Jeol XF-90Q (90MHz) nmr spectrometer. The chemical shifts (δ) are expressed in ppm relative to tetramethylsilane (TMS) and coupling constant (*J*) in Hertz. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. IR spectra were taken on a Nicolet FT IR-50X infrared spectrophotometer and reported in wave numbers ($cm^{-1}$). UV spectra were obtained on a Shimadzu UV-160A spectrophotometer. Melting points were determined with a "Thomas Hoover" melting (capillary method) apparatus and are uncorrected. Elemental analyses were carried out in the Central Laboratory of Zhongshan University.

The 2-alkyl-3-hydroxy-4(1*H*)-pyridinones (**1**) were synthesized following the procedure outlined in Ref.[7, 8]. Silver oxide was prepared on celite according to the method described in Ref.[9]. Unless otherwise stated, materials were obtained from commercial suppliers and without any further purification.

**2-Ethoxy-2-methyl-1,2-dihydro-pyridine-3,4-dione (2a).** Compound **1a** (6.25 g, 50 mmol) and $Ag_2O$ (60 mmol) were stirred in ethanol (400 ml) at 45 °C for 2 hr. The solid phase was removed by filtration and the solution was rotary-evaporated. The crude product was recrystallized from ether/hexane to give 7.1 g (42 mmol, 84%) of **2a** as bright yellow crystals, mp.97-98 °C. Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.51; N, 8.28. Found: C, 56.61; H, 6.55; N, 8.36. FAB MS: *m/z* 170 ($M+H^+$). IR (KBr): 3452, 3156, 1728, 1630 $cm^{-1}$. $^1$H NMR (DMSO-$d_6$, 90 MHz): δ 8.85 (1H, d, $J$ = 6.4 Hz, NH) ,7.62 (1H, dd, $J$ = 7.4, 6.4 Hz, C6-H), 5.16 (1H, d, $J$ = 7.4 Hz, C5-H), 3.47 (2H, m, $OCH_2$), 1.33 (3H, s, $CH_3$), 1.03 (3H, t, $J$ = 7.2 Hz, $CH_3$) ppm.

**2-Ethyl-2-methoxy-1,2-dihydro-pyridine-3,4-dione (2b).** Compound **1b** (6.95 g, 50 mmol) and $Ag_2O$ (60 mmol) were stirred in methanol (400 ml) at 20 °C for 2 hr. The crude product was recrystallized from ether/hexane to yield 7.5 g (44mmol, 89%) of **2b** as bright yellow crystals, mp.102-103 °C. Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.51; N, 8.28. Found: C, 56.72; H, 6.57; N, 8.37. FAB MS: *m/z* 170 ($M+H^+$). IR (KBr): 3423, 3163, 1721, 1630 $cm^{-1}$. $^1$H NMR (DMSO-$d_6$, 90 MHz): δ 9.16 (1H, d, $J$ = 6.4 Hz, N-H), 7.76 (1H, dd, $J$ = 7.4, 6.4 Hz, C6-H), 5.24 (1H, C5-H), 3.12 (3H, s, $OCH_3$),1.54-1.94 (2H, m, $CH_2$), 0.76 (3H, t, $J$ = 7.2 Hz, $CH_3$) ppm.

**Synthesis of the compounds 2c, 2d, and 2e.** The compound **2c, 2d,** and **2e** were synthesized in the same manner as that of compound **2a**.

**2-Ethyl-2-ethoxy-1,2-dihydro-pyridine-3,4-dione (2c).** Bright yellow crystals, mp.103-104 °C; yield 93%. Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.02; H, 7.10; N, 7.65. Found: C, 58.75; H, 7.23; N, 7.60. FAB MS: *m/z* 184 ($M+H^+$). IR (KBr): 3450, 3142, 1721, 1630 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 9.20 (1H, d, *J* = 6.4 Hz, NH), 7.75 (1H, dd, *J* = 7.4, 6.4 Hz, C6-H), 5.23 (1H, d, *J* = 7.4 Hz, C5-H), 3.44 (1H, m, C2-$OCH_2$), 3.21 (1H, m, C2-$OCH_2$), 1.86 (1H, m, C2-$CH_2$), 1.68 (1H, m, C2-$CH_2$), 1.07 (3H, q, *J* = 7.0 Hz, $CH_3$), 0.75 (3H, t, *J* = 7.4 Hz, $CH_3$) ppm.

**2-Ethyl-2-*n*-propoxy-1,2-dihydro-pyridine-3,4-dione (2d).** Bright yellow crystals, mp.125-126 °C; yield 91%. Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.91; H, 7.61; N, 7.11. Found: C, 60.63; H, 7.68; N, 7.15. FAB MS: *m/z* 198 ($M+H^+$). IR (KBr): 3444, 3142, 1721,1630 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 90 MHz): δ 9.12 (1H, d, *J* = 6.4 Hz, N-H ); 7.74 (1H, dd, *J* = 7.4, 6.4 Hz, C6-H); 5.23 (1H, d, *J* = 7.4 Hz, C5-H); 3.02-3.44 (2H, m, $OCH_2$); 1.22-2.01 (4H, m, $2CH_2$); 0.71-0.93 (6H, m, $2CH_3$) ppm.

**1,2-Dimethyl-2-methoxy-1,2-dihydro-pyridine-3,4-diones (2e).** Bright yellow crystals, mp.81-82 °C; yield 83%. Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.51; N, 8.28. Found: C, 56.68; H, 6.59; N, 8.24. FAB MS: *m/z* 170 ($M+H^+$). IR (KBr): 3177, 1700, 1630 $cm^{-1}$. $^1$HNMR (DMSO-$d_6$, 90 MHz): δ 7.76 (1H, d, *J* = 7.4 Hz, C6-H); 5.32 (1H, d, *J* = 7.4 Hz, C5-H); 3.29 (3H, s, $OCH_3$); 3.12 (3H, s, N-$CH_3$); 1.39 (3H, s, $CH_3$) ppm.

**2-Ethyl-3-hydroxy-6-(2`-hydroxyethylthio)-4(1*H*)-pyridinone (3a).** A mixture of **2c** ( 1.83 g, 10 mmol) and 2-mercaptoethanol (0.94 g, 12 mmol) were stirred in $CH_2Cl_2$ (150 ml) for 8 hr. The reaction solution was rotary-evaporated. The crude product was recrystallized from acetone/ethanol to give 1.76 g (82 mmol, 82 %) of **3a** as colorless crystals, mp.204-205 °C. Anal. Calcd. for $C_9H_{13}NO_3S$: C, 50.23; H, 6.05; N, 6.51; S, 14.9. Found: C, 50.14; H, 6.09; N, 6.48; S, 14.65. FAB MS: *m/z* 216 ($M+H^+$). IR (KBr) 3240, 1637, 1595, 1222 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 6.39 (1H, s, C5-H), 3.56 (2H, t, *J* = 7.0 Hz, $OCH_2$), 3.38 (1H, br, C-OH), 3.10 (2H, t, *J* = 7.0 Hz, S-$CH_2$), 2.58 (2H, q, *J* = 7.2 Hz, $CH_2$), 1.13 (3H, t, J = 7.2 Hz, $CH_3$) ppm.

**2-Ethyl-3-hydroxy-6-(phenylthio)-4(1*H*)-pyridinone (3b).** A mixture of **2c** ( 1.83 g, 10 mmol) and thiophenol (1.32 g, 12 mmol) were stirred in acetone (100 ml) for 24 hr at 25 °C . The resulting precipitate was collected by filtration and recrystallized from acetone/ethanol to afford 2.21 g (8.9mmol, 89 %) of **3b** as colorless crystals, mp.216-217°C. Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.16; H, 5.26; N, 5.66; S, 12.96. Found: C, 63.02; H, 5.43; N, 5.52; S, 12.90. FAB MS: *m/z* 248 ($M+H^+$). IR (KBr): 3184, 1630, 1581, 1518, 1222 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 7.34-7.42 (5H, m, Ph-H), 6.24 (1H, s, C5-H), 2.56 (2H, q, *J* = 7.2 Hz, $CH_2$),

1.09 (3H, t, $J$ = 7.2 Hz, $CH_3$) ppm.

**6-Anilino-2-ethyl-3-hydroxy-4(1*H*)-pyridinone (4a).** Pyridinedione **2c** (1.83 g, 10 mmol) and aniline (1.40 g, 15 mmol) were stirred in acetone (100 ml) for 8 hr at 25 °C . The reaction solution was rotary-evaporated. The crude product was recrystallized from acetone/ethanol to give 1.06 g (4.6 mmol, 46 %) of **2c** as colorless crystals, mp 210°C (decomp.). Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.83; H, 6.09; N, 12.17. Found: C, 67.52; H, 6.13; N, 12.08. FAB MS: *m/z* 231 ($M+H^+$). IR (KBr): 3416, 3410, 3121, 1644, 1623, 1595, 1222 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 90 MHz): δ 8.00 (1H, br, N-H), 6.75-7.38 (5H, m, Ph-H), 6.02 (1H, s, C5-H), 5.12 (2H, br, N-H, O-H exchangeable), 2.61 (2H, q, $J$ = 7.2 Hz, $CH_2$), 1.17 (3H, t, $J$ = 7.2 Hz, $CH_3$) ppm.

**2-Ethyl-3-hydroxy-6-(*p*-methylanilino)-4(1*H*)-pyridinone (4b).** Compound **4b** was prepared from **2c** and p-toluidine by the method described for **4a** in a yield of 66 % as colorless crystals, mp 222°C (decomp.). Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.85; H, 6.56; N, 11.48. Found: C, 68.43; H, 6.61; N, 11.42. FAB MS: *m/z* 245 ($M+H^+$). IR (KBr): 3289, 1637, 1609, 1510, 1222 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 8.13 (2H, br, N-H, O-H exchangeable), 7.01-7.30 (5H, m, Ph-H, N-H exchangeable), 6.00 (1H, s, C-H), 2.56 (2 H, q, $J$ = 7.6 Hz, $CH_2$), 2.20 (3 H, s, $(C_6H_4)$-$CH_3$), 1.14 (3 H, t, $J$ = 7.6 Hz, $CH_3$) ppm.

**6-(*p*-Bromoanilino)-2-ethyl-3-hydroxy-4(1*H*)-pyridinone (4c).** Compound **4c** was similarly prepared from **2c** and p-bromoaniline in 38 % yield, mp 220°C (decomp.). Anal. Calcd. for $C_{13}H_{13}BrN_2O_2$: C, 50.49; H, 4.21; N, 9.06; Br, 25.89. Found: C, 50.25; H, 4.26; N, 8.98; Br, 25.86. FAB MS: *m/z* 310,312 ($M^+$). IR(KBr): 3430, 3240, 1665, 1616, 1588, 1222, 533 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 90 MHz): δ 8.52 (2H, br, N-H, O-H exchangeable), 7.21-7.70 (5H, m, 4Ph-H, N-H exchangeable), 6.11 (1H, s, C5-H), 2.62 (2H, q, $J$ = 7.2 Hz, $CH_2$), 1.13 (3H, t, $J$ = 7.2 Hz, $CH_3$) ppm.

## ACKNOWEDGEMENT

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