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A CONVENIENT APPROACH TO 1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLATES BY ELECTRO-OXIDATIVE FORMATION OF ENAMINE MOIETY

Sigeru TORII,* Hiroshi OKUMOTO, and Long He XU
Department of Applied Chemistry, Faculty of Engineering
Okayama University, Tsushima Naka, Okayama 700, JAPAN

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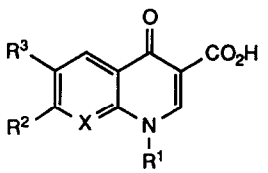
Abstracts: A practical synthetic approach to the drugs of current interest, 1,4-dihydro-4-oxo-quinoline-3-carboxylic acids, has been accomplished through the electro-oxidative formation of double bond adjacent to the nitrogen atom. The efficiency was shown by the introduction of some representative substituents at the C7 position.

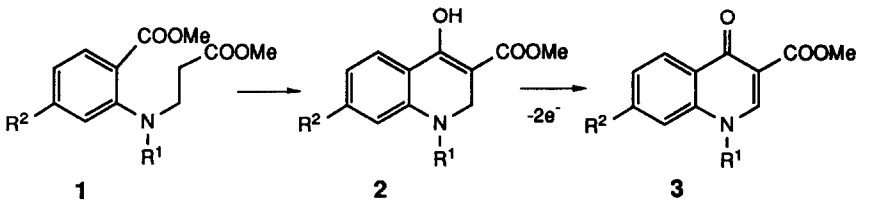
Since the discovery of the prototypical quinolinone antibiotic, nalidixic acid, in 1962,[1] a large number of its congeners have been synthesized and evaluated, and their structure-activity relationship has been reviewed.[2] In particular, during the last decade, a considerable attention has been paid to the structural modifications which have led to new analogues with dramatic improvement of antibacterial potency. These investigations have shown that the pyridone carboxylic acid is the indispensable framework for the antibacterial activity which also highly depends upon the substituents.[2] These modifications have been a subject of considerable current interest.



Nalidixic Acid : X=N, R^1=Et, R^2=Me, R^3=H
New Analogues : X=CH, R^1=alkyl,
R^2; R^3=N-hetero rings; F or H, combined by hetero rings, etc.

With regard to synthetic chemistry, most of the efforts have been focused on the following aspects. 1) Construction of the highly oxidized skeleton. 2) Introduction of a variety of substituents including halogen atoms at the C6 position and nitrogen appendages at the C7 position. In contrast to the intensive studies on the structure-activity relationship, only a few efforts have been directed toward the synthesis of the quinolinone skeleton. Previous synthetic routes to these molecules can be classified into only four paths,[3] some of which require high temperature (> 200 °C) and others involve inconvenient procedures.

We focused our attention on the development of a more convenient method for the construction of the quinolinone skeleton. Herein, we wish to report a new and general method to synthesize the highly oxidized skeleton of the quinolinone 3-carboxylates as shown in scheme 1, wherein the electro-oxidation plays an essential role.



1 2 3

a: $R^1=R^2=H$; **b**: $R^1=H$, $R^2=Cl$; **c**: $R^1=Ac$, $R^2=H$; **d**: $R^1=COOMe$, $R^2=H$;
e: $R^1=Ac$, $R^2=Cl$; **f**: $R^1=COOMe$, $R^2=Cl$

scheme I

The hitherto reported oxidations of homologues of **2** require quinone oxidants such as chloranil,[4] or addition of molecular bromine followed by alkaline work up.[5] However, these methods do not give satisfactory results in any cases. Due to the lack of a practically useful oxidation method, the synthetic path **1** → **2** → **3** has attracted less attention in spite of its versatility and generality. An electro-oxidation seemed to be expedient for this purpose, because a carbenium ion would be easily generated by two-electron oxidation of nitrogen containing compounds such as **2**, and the acidic proton on 3-position would be immediately deprotonated to form **3**. Syntheses of simple enamides and carbamates have been described by the anodic oxidation,[6] where double bonds are formed at the proper position in high yields. Some of them accompany decarboxylation[7] and others contain two sequences,[8] in which a methoxy group is anodically introduced to the position α to the nitrogen atom and acid catalyzed elimination of methanol produces the carbon-carbon double bond. However, there is no report on utilizing the electro-oxidation method to construct directly such a highly oxidized quinolinone skeleton. Electro-oxidation as a practical and simple oxidation method is very attractive for our present purpose.

The diesters **1a** and **1b** were obtained according to the procedure in the literature.[9] The β-ketoesters **2** were prepared by protecting the amino function as an amide followed by Dieckmann cyclization. The reason of the protection is to improve the yield of the cyclization, because it is reported that the yield of the cyclization of free secondary amines is generally low.[9] The protection of amino group by reaction with acetyl chloride or methyl chloroformate was carried out in

the usual manner in almost quantitative yields. After purification of the products by chromatography, the Dieckmann cyclization was performed by using sodium hydride as a base in THF or DMSO, wherein choice of the solvent was crucial in obtaining good yields. The desired bicyclic compounds **2** were produced in the satisfactory yields as indicated in Table 1.

Table 1. Conversion of diester **1** to ketoester **2**

1 $\xrightarrow[\text{2) NaH}]{\text{1) AcCl or ClCOOMe}}$ **2**

step 1		step 2	
1	**1** (%)	solvent	**2** (%)
a	**c** (97)	THF	**c** (79)
a	**d** (91)	THF	**d** (69)
b	**e** (98)	DMSO	**e** (77)
b	**f** (98)	THF	**f** (62)

Subsequently, the electro-oxidation of **2c** was carried out by using ammonium salts as a supporting electrolyte. Some of the results are collected in Table 2.

Table 2. Eletrolysis of **2c**.

Entry	Electrolyte	Solvent	Electricity (F / mol)	**3a**, %
1	Et_4NOTs	AcOH	2.5	58
2	Et_4NOTs	AcOH / t-BuOH (7 / 1)	2.5	63
3	Bu_4NBr	AcOH / t-BuOH (7 / 1)	2.5	trace
4	Bu_4NClO_4	AcOH / t-BuOH (7 / 1)	3.0	50
5	Et_3N	AcOH / t-BuOH (7 / 1)	2.5	30
6	Et_4NOTs	AcOH / t-BuOH (7 / 1)	2.2	67

Reaction conditions: (C) - (C), 3.3 mA / cm^2, undivided cell

Since, in our laboratory, typical electrolysis conditions for nitrogen containing substrates have already been elaborated in the synthesis of indole derivatives,[10] we employed the mixed solvent system composed of acetic acid and *tert*-butanol.

Among the ammonium salts examined, tetraethylammonium tosylate and tetrabutylammonium perchlorate were effective as shown in entries 2 and 4. In particular, the tosylate gave the best result and 67% yield of **2a** was obtained after passage of 2.2 F/mol of electricity (entry 6). The presence of a small amount of *tert*-butanol in acetic acid improved the oxidation (compare entries 1 and 2). Use of the AcOH/*tert*-BuOH-Et_4NOTs-(C) system, which was found to be the best conditions, led to the formation of **3a** as a predominant product from **2c** by two-electron oxidation. It should be noted that the electro-oxidation product **3a** contains no acetyl protecting group. When the 2.2 F/mol of electricity was passed, the corresponding acetylated compound **3c** together with **3a** can be detected, however, continuous stirring of the reaction mixture at ambient temperature for 1 day without passing electricity afforded the deprotected substrate **3a**. Fortunately, the acetyl moiety could be removed in the same flask. Acetic acid as solvent would cause such a concurrent deprotection. Hence, this anodic oxidation system was utilized for the following substrates.

Table 3. Electrolysis of **2c** - **2f** to obtain **3a** - **3b**

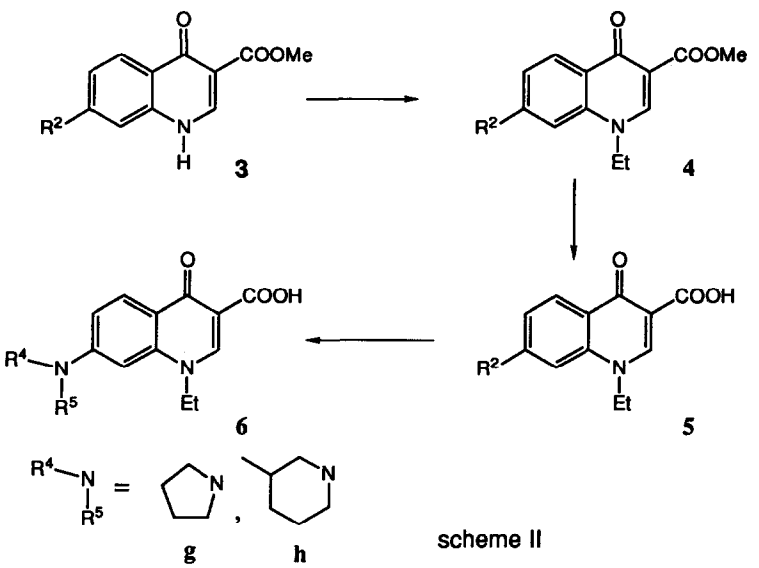
starting material	**2c**	**2d**	**2e**	**2f**
product (%)	**3a** (67)	**3a** (90)	**3b** (82)	**3b** (86)

conditions: AcOH/t-BuOH (7/1), Et_4NOTs, 3.8-3.3 mA/cm^2, 2.2 F/mol

The electrolysis of the β-ketoesters **2d** as well as both **2e** and **2f** which contain a chlorine atom at C7 was attempted to introduce amino pendants in the final stage. Every anodic reaction produced the desired enamides **3a** and **3b** in high yields as shown in Table 3. In these cases, the free amine was again released under the reaction conditions. The anodic oxidation of the carbamates **2d** and **2f** gave better yields of **3a** and **3b**, respectively, in comparison with the cases employing acetamides **2c** and **2e**. A slight change of the electron density of the nitrogen atom, from which the initial active species are anodically generated, probably influences the reaction course. Furthermore, the oxidation of the chloride **2e** proceeded more efficiently than that of the unsubstituted substrate **2c**. Based on these results, we suppose that the present oxidation method may be extended to other homologues of **2** having various substituents observed in commercially utilized drugs.

The remaining steps to complete the synthesis of antibiotics are introduction of the alkyl substituents on nitrogen atom and displacement of chlorine atom with nitrogen pendants. These manipulations of the functionalities could be achieved by

the established protocols.[11] Thus, at first, **3a** was treated with ethyl iodide in the presence of potassium carbonate in DMF. The alkylation proceeded smoothly to provide the expected tertiary amine **4a** and the corresponding chloride **3b** also gave the ethylated amine **4b**. These crude esters were hydrolyzed with sodium hydroxide to afford the carboxylic acid **5a** and **5b** quantitatively. Due to the initial discovery of the antibacterial activity of **5b**, nalidixic acid was prepared and the chemistry of the quinolinone carboxylic acid drugs has been extended.[1,2] Substitution of the chloride **5b** were successfully attained by simply heating at 100 °C with pyrrolidine and 3-methylpiperidine. As a result, the final target molecules **6g** and **6h** were obtained in good yields.



scheme II

The characteristics of our method can be summarized as follows. Either cumbersome procedures or expensive, toxic reagents are not involved in each stage. Electro-oxidation as a key reaction in this synthesis can be carried out in a simple beaker type cell, which requires neither a complicated procedure nor special care. Every step proceeds in a high yield and electrolysis products can be isolated by filtration and purified by recrystallization. The newly developed method may provide a practical and convenient route to the quinolinone antibiotics.

Acknowledgment; We are grateful to the SC-NMR Laboratory of Okayama University for obtaining high resolution NMR.

Experimental Section

^1H and ^{13}C NMR spectra were recorded in the indicated solvents on varian VXR 200 (200 MHz for ^1H and 50 MHz for ^{13}C) spectrophotometers. The chemical shifts are given in ppm relative to $CHCl_3$ (7.26 ppm, ^1H), $CDCl_3$ (77 ppm, ^{13}C), DMSO-d_6 (2.49 ppm, ^1H and 39.5 ppm, ^{13}C). When CF_3COOD was used as a solvent to obtain NMR spectra, TMS was used as an internal standard. Jasco FT/IR-5000 infrared spectrophotometer was used to determine IR spectra. Elemental analyses were performed on a Yanagimoto CH analyzer MT-3.

1-Acetyl-1,2-dihydro-4-hydroxy-quinoline-3-carboxylic acid methyl ester (**2c**)

To a mixture of diester **1a** (0.980 g, 4.09 mmol), pyridine (0.4 ml, 4.8 mmol), and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine in dichloromethane (5 ml) was added dropwise acetyl chloride (0.32 ml, 4.5 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h and then poured into ice-water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel to afford 1.22 g of acetylated product.

The acetylated product (1.22 g) dissolved in THF (6 ml) was added into a suspension of sodium hydride (172.9 mg, 4.32 mmol) in THF (6 ml) and the mixture was heated to refluxing for 10 h. The resulting mixture was cooled to room temperature and then poured into ice-water. The product was extracted with ethyl acetate and dried over magnesium sulfate. Concentration followed by purification by chromatography gave **2c** (0.80 g) in 79.2% yield. The analytical sample was prepared by recrystallization from ethyl acetate/hexane. IR (KBr) 1670, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H), 3.80 (s, 3 H), 4.61 (s, 2 H), 7.20-7.28 (m, 2 H), 7.39 (dd, J = 1.6, 7.4 Hz, 1 H), 7.76 (dd, J = 1.6, 8.2 Hz, 1 H), 11.94 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.28, 40.00, 51.80, 97.24, 123.76, 124.49, 124.72, 125.41, 130.76, 139.53, 162.75, 169.01, 170.21; Anal. Cacld for $C_{13}H_{13}NO_4$: C, 63.16; H, 5.26; N, 5.67. Found: C, 63.08; H, 5.20; N, 5.72.

1-Methoxycarbonyl-1,2-dihydro-4-hydroxy-quinoline-3-carboxylic acid methyl ester (**2d**)

To a mixture of **1a** (1.99 g, 8.4 mmol), sodium hydrogen carbonate (1.1 g) in ethanol (20 ml) and water (5 ml) was added methyl chloroformate (1.2 ml, 1.5 mmol) and the whole mixture was stirred at room temperature overnight. The resulting mixture was poured into ice-water and extracted with ethyl acetate. The combined extracts were washed with brine and dried over sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel to afford 1.96 g of the corresponding carbamate.

A mixture of the carbamate (1.96 g) and sodium hydride (0.291 g, 7.3 mmol) in THF (30 ml) was refluxed for 3 h. The mixture was poured into ice-water, extracted with ethyl acetate, and then dried over sodium sulfate. After removal of the solvent, the residue was purified by chromatography to give 1.2 g of **2d** in 68.9% yield. The analytical sample was prepared by recrystallization from ethyl acetate/hexane. IR (KBr) 1713, 1667, 1624 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3 H), 3.84 (s, 3 H), 4.60 (s, 2 H), 7.18 (dt, J = 1.16, 7.57 Hz, 1 H), 7.40 (dt, J = 1.67, 7.82 Hz,

1 H), 7.62 (br d, J = 8.3 Hz, 1 H), 7.77 (dd, J = 1.67, 7.82 Hz, 1 H), 11.98 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 41.25, 51.82, 53.24, 95.64, 123.46, 123.55, 124.36, 124.44, 131.10, 139.31, 154.16, 163.09, 170.35; Anal. Cacld for $C_{13}H_{13}NO_5$: C, 59.32; H, 4.94; N, 5.32. Found: C, 59.51; H, 4.87; N, 5.39.

1-Acetyl-7-chloro-1,2-dihydro-4-hydroxy-quinoline-3-carboxylic acid methyl ester (**2e**)

To a mixture of **1b** (1.62 g, 5.98 mmol), pyridine (0.6 ml) and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine in dichloromethane (10 ml) was added acetyl chloride (0.6 ml, 8.4 mmol) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The residue was chromatographed to afford 1.83 g of acetylated product.

To a suspension of sodium hydride (0.26 g, 6.49 mmol) in DMSO (15 ml) was added the acetylated product (2.00 g, 6.38 mmol) dissolved in DMSO (15 ml) at room temperature. After 30 min of stirring, the resulting mixture was poured into ice-water, extracted with ethyl acetate, and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by chromatography to give 1.38 g of **2e** in 76.8% yield. Recrystallization from ethyl acetate/hexane afforded the analytical sample. IR (KBr) 1700, 1657, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3 H), 3.84 (s, 3 H), 4.60 (s, 2 H), 7.23 (dd, J = 2.0, 8.50 Hz, 1 H), 7.38 (br, 1 H), 7.72 (d, J = 8.50 Hz, 1 H), 11.92 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.53, 40.60, 52.02, 122.87, 124.08, 125.66, 125.78, 125.86, 136.73, 140.45, 162.17, 169.22, 170.15; Anal. Cacld for $C_{13}H_{12}ClNO_4$: C, 55.42; H, 4.26; N, 4.97. Found: C, 55.52; H, 4.15; N, 5.02.

1-Methoxycarbonyl-7-chloro-1,2-dihydro-4-hydroxy-quinoline-3-carboxylic acid methyl ester (**2f**)

A mixture containing **1b** (222 mg, 0.82 mmol) and sodium hydride (48 mg, 12 mmol) in THF (3 ml) was stirred for 1 h at room temperature. Methyl chloroformate (0.5 ml) was added dropwise and then the mixture was stirred at 50 °C for 48 h. Most of the solvent was evaporated and the resultant mixture was dissolved in ethyl acetate. The organic layer was washed with ice-water and dried over sodium sulfate. After removal of the solvent, the residue was purified by chromatography on silica gel to give carbamate (265 mg).

To a suspension of sodium hydride (134 mg, 3.34 mmol) in THF (5 ml) was added dropwise the carbamate (0.968 g, 2.94 mmol) at 0 °C and then the mixture was stirred at that temperature for 10 h. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The remaining oil was purified by chromatography on silica gel to give 0.54 g of **2f** in 61.8% yield. The analytical sample was obtained by recrystallization from ethyl acetate/hexane. IR (KBr) 1711, 1665, 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3 H), 3.48 (s, 3 H), 4.60 (s, 2 H), 7.15 (dd, J = 1.93, 8.35 Hz, 1 H), 7.68 (d, J = 8.35 Hz, 1 H), 7.69 (d, J = 1.93 Hz, 1H), 11.96 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 41.38, 51.93, 53.50, 95.40, 121.74, 123.57, 124.59, 125.51, 137.09, 140.20, 153.87, 162.22, 170.19; Anal. Cacld for $C_{13}H_{12}ClNO_5$: C, 52.44; H, 4.03; N, 4.71. Found: C, 52.45; H, 3.96; N, 4.72.

1,4-dihydro-4-oxo-quinoline-3-carboxylic acid methyl ester (**3a**)

An undivided cell fitted with two carbon electrodes was charged with a mixture of **2d** (223.4 mg, 0.85 mmol), tetraethylammonium tosylate (100.9 mg, 0.33 mmol), *tert*-butanol (1 ml), and acetic acid (7 ml). The solution was electrolyzed under constant current of 3.3 $mAcm^{-2}$ at room temperature. After 2.2 $Fmol^{-1}$ of electricity was passed, the reaction mixture was continuously stirred for one day at room temperature. The resulting mixture was concentrated and the residue was dissolved in hot dichloromethane. After the mixture was cooled to room temperature, the white precipitates were collected by filtration. The obtained solids were washed with cold dichloromethane and dried to afford 104.9 mg of **3a** and the combined filtrates and washings were concentrated and chromatographed to afford 49.3 mg of **3a**. The total yield of **3a** was 89.5%. The analytical sample was prepared by additional recrystallization from DMF. IR (KBr) 3400, 1711, 1628, 1586, 1537 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.73 (s, 3 H), 7.39 (br t, J = 8.2 Hz, 1 H), 7.59-7.74 (m, 2 H), 8.15 (d, J = 7.8 Hz, 1 H), 8.57 (d, J = 6.8 Hz, 1 H), 12.4 (br, 1 H); ^{13}C NMR (DMSO-d_6) δ 51.12, 109.44, 118.81, 124.74, 125.63, 127.26, 132.43, 138.96, 145.13, 165.38, 173.42; Anal. Cacld for $C_{11}H_9NO_3$: C, 65.00; H, 4.43; N, 6.90. Found: C, 64.70; H, 4.41; N, 7.02.

7-Chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid methyl ester (**3b**)

A solution of **2e** (0.758 g, 2.69 mmol), tetraethylammonium tosylate (302 mg, 0.91 mmol), *tert*-butanol (3 ml) and acetic acid (21 ml) was electrolyzed in an undivided cell fitted with two carbon electrodes under constant current density of 3.3 $mAcm^{-2}$ at room temperature. After 2.2 $Fmol^{-1}$ of electricity was passed, the resulting mixture was continuously stirred at room temperature for one day. Most of the solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane. The precipitates were collected by filtration, washed with cold dichloromethane, and dried to give 0.524 g of **3b** in 82.2% yield. The analytical sample was prepared by recrystallization from DMF. IR (KBr) 3398, 1701, 1615, 1589, 1528 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 4.24 (s, 3 H), 7.97 (dd, J = 1.78, 8.95 Hz, 1 H), 8.21 (d, J = 1.78 Hz, 1 H), 8.65 (d, J = 8.95 Hz, 1 H), 9.36 (s, 1 H), 11.75 (s, 1 H); ^{13}C NMR (CF_3CO_2D) δ 49.14, 100.53, 113.98, 115.08, 121.56, 126.95, 135.55, 141.60, 141.70, 163.29, 168,85; Anal. Cacld for $C_{11}H_8ClNO_3$: C, 55.58; H, 3.37; N, 5.89. Found: C, 55.55; H, 3.33; N, 5.96.

The corresponding carbamates **2c** and **2f** were also converted to **3a** and **3b** in the same manner in 67% and 86% yields respectively.

1-Ethyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (**5a**)

A mixture of **3a** (198 mg, 0.98 mmol), potassium carbonate (472 mg, 3.42 mmol), and iodoethane (1 ml) in DMF (1.5 ml) was heated at 75-80 °C with stirring overnight under argon atmosphere. The mixture was concentrated to dryness and extracted with dichloromethane. The dichloromethane layer was washed with water, dried, and evaporated. The crude ester **4a** (231.5 mg) was used in the successive reaction without purification.

A solution of the crude ester **4a** (232 mg) in 2*N* sodium hydroxide (2.5 ml) was refluxed with stirring for 3 h. The mixture was acidified with 5% hydrochloric

acid and the resulting precipitates were filtered off. The solids were washed with water and dried to give 195 mg of **5a** in 91.7% yield. The analytical sample was obtained by recrystallization from ethanol. IR (KBr) 3420, 1717, 1618, cm^{-1}; ^1H NMR (CF_3CO_2D) δ 1.85 (t, J = 7.26 Hz, 3 H), 5.01 (q, J = 7.26 Hz, 2 H), 8.11 (t, J = 7.8 Hz, 1 H), 8.32 (d, J = 8.6 Hz, 1 H), 8.40 (t, J = 7.8 Hz, 1 H), 8.85 (d, J = 8.6 Hz, 1 H), 9.51 (s, 1 H); ^{13}C NMR (CF_3CO_2D) δ 9.43, 49.13, 100.19, 111.55, 117.39, 122.52, 126.42, 134.66, 136.06, 145.12, 165.99, 169.09; Anal. Cacld for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.07; N, 6.45. Found: C, 66.28; H, 4.94; N, 6.48.

1-Ethyl-7-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (**5b**)

The corresponding 7-chloro compound **5b** was obtained by the same procedure with above.

IR (KBr) 3428, 1717, 1609 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 1.84 (t, J = 7.3 Hz, 3 H), 4.96 (q, J = 7.3 Hz, 2 H), 8.04 (d, J = 8.9 Hz, 1 H), 8.31 (s, 1 H), 8.76 (d, J = 8.9 Hz, 1 H), 9.50 (s, 1 H); ^{13}C NMR (CF_3CO_2D) δ 8.75, 48.65, 100.09, 113.74, 115.14, 123.11, 126.91, 136.15, 142.53, 145.49, 165.08, 168.26; Anal. Cacld for $C_{12}H_{10}ClNO_3$: C, 57.26; H, 3.98; N, 5.57. Found: C, 57.05; H, 3.87; N, 5.65.

1-Ethyl-7-pyrrolidinyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (**6g**)

Excess of pyrrolidine (0.2 ml) was added into a solution of **5b** (96.6 mg, 0.38 mmol) in *N*-methyl-2-pyrrolidinone (1 ml) and the mixture was stirred at 100 °C. After being stirred at that temperature under argon atmosphere for 20 h, the solution was evaporated to dryness under reduced pressure. Ethanol (1 ml) was added into the residue and the mixture was boiled for 5 min and cooled. The precipitated solids were filtered, washed with ethanol, and dried to afford 92 mg of the 3-carboxylic acid **6h** in 83.8% yield. The analytical sample was obtained by further recrystallization from ethanol. IR (KBr) 3440, 1707, 1628 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 1.78 (t, J = 7.2 Hz, 3 H), 2.30 (br, 4 H), 3.73 (br, 4 H), 4.72 (q, J = 7.2 Hz, 2 H), 7.39 (d, J = 9.45 Hz, 1 H), 8.51 (d, J = 9.45 Hz, 1 H), 9.13 (s, 1 H), 11.71 (s, 2 H); ^{13}C NMR (CF_3CO_2D) δ 7.83, 20.05 (2 carbons), 44.76 (2 carbons), 47.26, 96.56, 106.89, 113.57 (2 carbons), 123.26, 138.11, 143.75, 149.64, 164.20, 166.76; Anal. Cacld for $C_{16}H_{18}N_2O_3$: C, 67.13; H, 6.29; N, 9.79. Found: C, 67.02; H, 6.32; N, 9.82.

1-Ethyl-7-(3-methylpiperidinyl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (**6h**)

This substrate was prepared by the above mentioned procedure in 76% yield. The analytical sample was prepared by recrystallization from ethanol. IR (KBr) 3470, 1717, 1613 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.92 (d, J = 6.54 Hz, 3 H), 1.37 (t, J = 7.08 Hz, 3 H), 1.46-1.86 (m, 4 H), 2.54-2.69 (m, 1 H), 2.82-3.00 (m, 1 H), 3.30-3.5 (m, 1 H), 3.85-4.1 (m, 1 H), 4.50 (q, J = 7.08 Hz, 2 H), 6.87 (d, J = 1.90 Hz, 1 H), 7.28 (dd, J = 1.90, 9.34 Hz, 1 H), 8.07 (d, J = 9.34 Hz, 1 H), 8.82 (s, 1 H), 15.84 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 14.22, 18.99, 24.24, 30.21, 32.48, 47.36, 48.43, 54.44, 97.59, 106.60, 114.59, 115.55, 127.11, 141.30, 148.25, 154.16, 166.62, 176.20; Anal. Cacld for $C_{18}H_{22}N_2O_3$: C, 68.79; H, 7.01; N, 8.92. Found: C, 68.64; H, 7.62; N, 8.99.

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