# A Synthesis of 5-Amino- and 5-Hydroxy-1-ethyl-1,4-dihydrio-4-oxo-3-quinolinecarboxylic Acids and Their Derivatives



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The synthesis and antimicrobial activity of 5-amino- and 5-hydroxy-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids and their derivatives have been investigated. The 5-hydroxy-3-quinolinecarboxylic acids were prepared by thermal cyclization of 3-oxocyclohexenylaminomethylenemalonates followed by aromatization with iodine-ethanol, ethylation and hydrolysis of products. The 5-amino derivatives were prepared by several steps involving novel aromatization of isoxazole intermediates.

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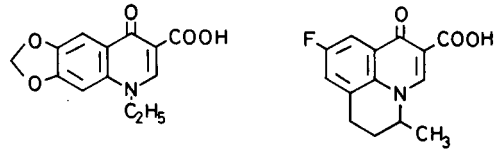
The fact that the strong antibacterial agents such as oxolinic acid (**1a**) and flumequine (R802) (**1b**) have common 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid structure raised the interest in the synthesis and study of the related quinolinecarboxylic acid derivatives. Since then, a number of 6-, 7-, and 8-substituted 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids have been prepared and studied extensively (1), but very few reports are available on the 5-substituted isomers, probably because of the difficulty of preparation. Especially the preparation of the 5-amino- and 5-hydroxy-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids has not been reported to date. 5-Nitro and 5-alkoxyquinolinecarboxylic acids are thought to be desirable synthetic precursors of 5-amino and 5-hydroxy derivatives. Recently, Agui and co-workers prepared (2) some 5-substituted 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids by the thermal cyclization of the corresponding *m*-substituted anilinomethylenemalonates using polyphospholic ethyl ester. The method led to a mixture of the isomeric 5- and 7-substituted quinolines, from which the 5-nitro isomer could be isolated only in 1% yield when a nitro substituent was present and the 5-methoxy isomer could not be obtained at all in the case when an alkoxy substituent was present. Very recently, Frank and Rakoczy have reported (3) the preparation of 5-nitro-6,7-methylenedioxy-4-oxoquinolinecarboxylic acids by the direct nitration of the corresponding acids and made them into the 5-aminoquinolinecarboxylic acids, but this method is not applicable to the 6- or 7-unsubstituted quinolinecarboxylic acids. We now found a novel preparation of 5-amino- and 5-hydroxy-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids involving a thermal cyclization of 3-oxocyclohexenylaminomethylenemalonates and subsequent aromatization reaction. The present paper describes their preparation and antimicrobial activities and these are compared with the other known 5-substituted and 5-unsubstituted quinolinecarboxylic acids.

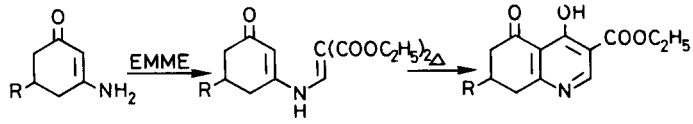


1a 1b

Figure I

The starting ethyl 4-hydroxy-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylates (**4a,b**) were obtained by a method similar to the preparation of the substituted ethyl 1,4-dihydro-4-oxonicotianates reported by Agui (4). Thus, the thermal cyclization of the enaminomethylenemalonates **3a,b** readily obtained from the cyclic $\beta$-aminovinylketones **2a,b** and ethoxymethylenemalonate (EMME) was carried out by refluxing a biphenylether solution of them for 15 minutes to give the corresponding quinolinecarboxylates **4a,b** in high yields (Scheme I)

Scheme I



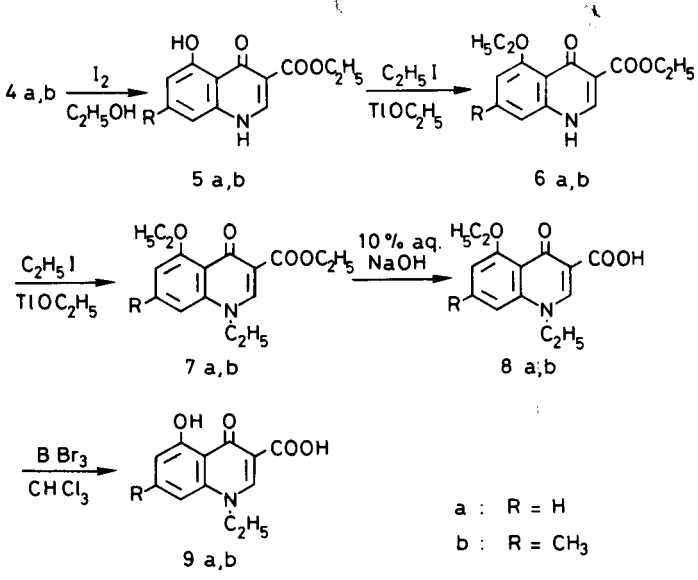
2 a,b 3 a,b 4 a,b

a : R = H

b : R = $CH_3$

The synthesis of the desired 5-ethoxy- (**8a,b**) and 5-hydroxy-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (**9a,b**) is outlined in Scheme II. Aromatization of **4a,b** by the previously reported method (5) using iodine in ethanol gave high yields of the 1,4-dihydro-5-hydroxy-4-oxo-3-quinolinecarboxylates (**5a,b**). In a recent paper, we have reported a useful *N*-alkylation of ethyl 1,4-dihydro-4-oxopyridine-3-carboxylates *via* their thallium(I) salt (6). The method is also quite useful for the alkylation of **5a,b**.

Scheme II

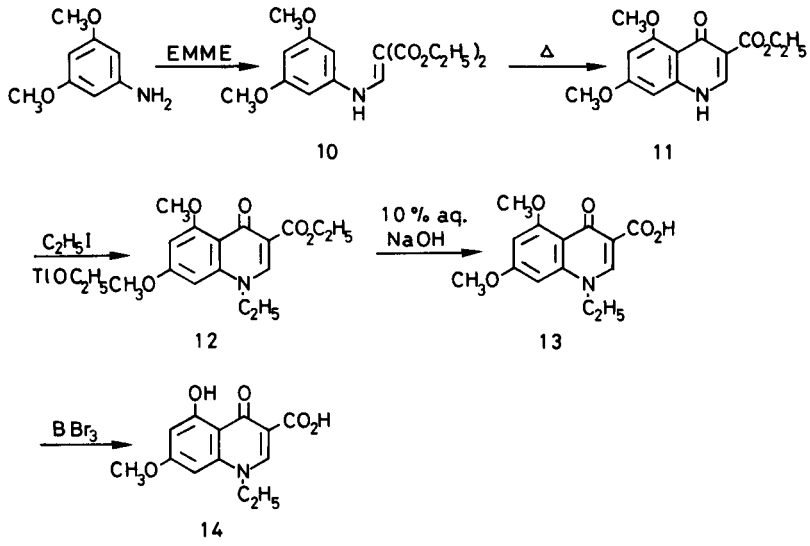



Treatment of monothallium(I) salts of **5a,b** with ethyl iodide gave the *O*-ethylated compounds **6a,b** selectively and treatment of the *N,O*-di-thallium(I) salts with ethyl iodide gave *N,O*-diethylated compounds **7a,b** in high yields. The esters **7a,b** were hydrolyzed quantitatively by the treatment with 10% aqueous sodium hydroxide at 90-100° for 2.5 hours to give **8a,b**. Deethylation of **8a,b** by boron tribromide in chloroform at 40° for 1 day gave high yields of **9a,b**. The related 5-hydroxy-7-methoxyquinolinecarboxylic acid (14) was prepared in a five step sequence starting with 3,5-dimethoxyaniline as shown in Scheme III. Condensation of 3,5-dimethoxyaniline with EMME gave 3,5-dimethoxyanilinomethylenemalonate (**10**), which was converted into ethyl 1,4-dihydro-5,7-dimethoxy-4-oxo-3-quinolinecarboxylate (**11**) by thermal cyclization. The ester **11** was ethylated by the previous method using thallium(I) ethoxide and ethyl iodide to give the *N*-ethylated ester **12**. Compound **12** was hydrolyzed by treating with 10% aqueous sodium hydroxide at 90-100° for 2.5 hours to give the quinolinecarboxylic acid **13**. 5-Hydroxy-7-methoxyquinolinecarboxylic acid (**14**) was obtained by treatment of **13** with boron tribromide in chloroform at 40° for 2 days.

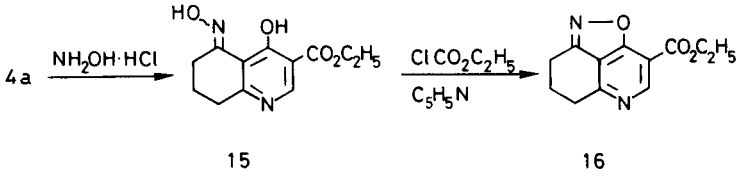
The Semmler-Wolff reaction of cyclohexenone oxime derivatives is well known as a useful method for the preparation of the aromatic amino compounds (7). Although application of this reaction to ethyl 4-hydroxy-5-oxo-5,6,7,8-tetrahydro-3-quinolinecarboxylate (**4a**) seems to be a simple route to the 5-aminoquinolinecarboxylate, no attempt has been made. Therefore, we planned to make oxime or oxime derivatives of **4a** and to examine their Semmler-Wolff aromatization. Ketone **4a** was treated with hydroxylamine·hydrochloride-sodium acetate in refluxing ethanol-water to give its oxime **15**. Treatment of **15** with ethyl chloroformate-pyridine in chloroform gave a high yield of the corresponding isoxazole **16**, whose structure was proven by its ir, nmr and elemental analyses. The oxime **15** or isoxazole **16** was submitted to the effective Semmler-Wolff condition using 1-ethoxyvinyl acetate in the presence of catalytic amounts of *p*-toluenesulfonic acid (8) to give unidentified compounds instead of the desired ethyl 5-acetamido-1,4-dihydro-4-oxo-3-quinolinecarboxylate.

Finally, 5-aminoquinoline derivatives **22** and **23** were synthesized in a four step sequence starting with the isoxazole intermediate **16** as shown in Scheme V. The isoxazole

Scheme III



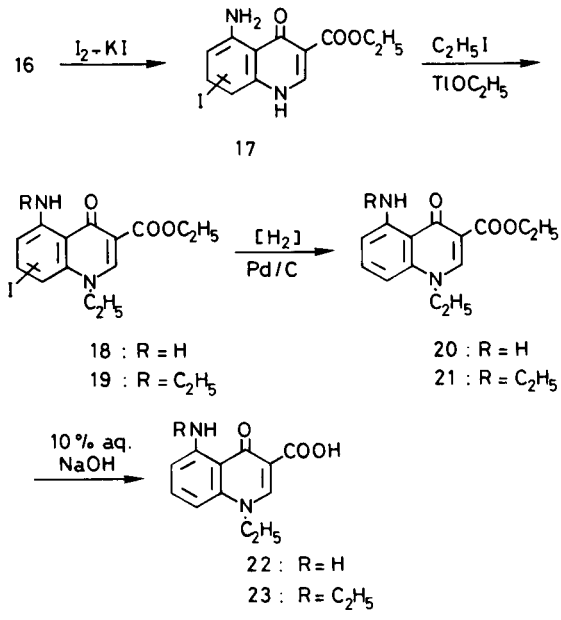
Scheme IV



15 16

**16** was aromatized successfully with iodine-potassium iodide in refluxing ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid. Similar conditions have been known to be useful for the oxidation of acyclic $\alpha,\beta$-unsaturated carbonyl compounds into their isoxazoles (9). This is the first example of a direct aromatization of cyclohexenone oxime derivatives with iodine-potassium iodide.

Scheme V



17

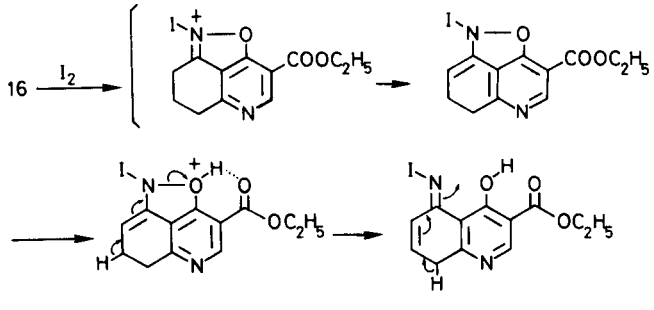
18 : R = H
19 : R = $C_2H_5$

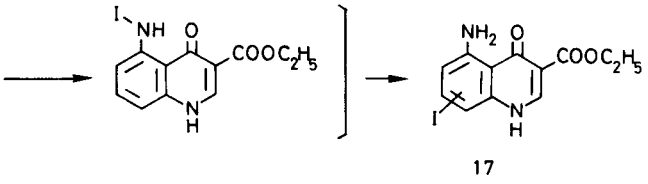
20 : R = H
21 : R = $C_2H_5$

22 : R = H
23 : R = $C_2H_5$

Although the exact mechanism is not clear, the initial iodination of the nitrogen atom of the isoxazole ring followed by an imine-enamine tautomerization, acid-catalyzed N-O bond fission, and final iodination of the produced 5-amino aromatic compound are postulated for the formation of **17** (Scheme VI).

Scheme VI





17

Then the 5-amino ester **17** was alkylated by the previous method using thallium(I) ethoxide and ethyl iodide to give mainly the *N*-ethylated ester **18** accompanied by a small amount of *N,N'*-diethylated ester **19**. The mixture was catalytically hydrogenated with 5% palladium-carbon in ethanol without separation of each isomer to give a mixture of *N*-ethylated **20** and *N,N'*-diethylated esters **21** in 63 and 14% yields, respectively. The alkaline hydrolysis of these esters **20** and **21** with 10% aqueous sodium hydroxide led to a quantitative yield of the corresponding acids **22** and **23**.

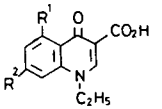
All the compounds reported herein have been screened *via in vitro* antibacterial activity against Gram-positive and Gram-negative bacteria (Table I). The results of the other known 5-substituted and 5-unsubstituted 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (runs 1, 6, 9, 12, and 13) have been compared. Generally, 5-substituted 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids have been known to exhibit only slight or no activity (2) probably due to the fracture of the planar structure of the compound because of the C-5 substituent. In contrast, upon introduction of hydroxyl or amino function into C-5 position, the reactivity increases significantly, almost reaching that of the corresponding 5-unsubstituted quinolinecarboxylic acids as observed in runs 2, 3, 7, 10, and 13. Substitution of the hydroxyl function (runs 5, 8, and 11) reduces the antibacterial activity again. The promising activity of 5-hydroxy- and 5-aminoquinolinecarboxylic acids (runs 2, 3, 7, 10, and 13) provides a possibility to obtain stronger antibacterial agents by testing the 5-hydroxy and 5-amino derivatives of nalidixic acid and its congeners.

## EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured with a Hitachi EPI-G2 spectrophotometer in chloroform unless otherwise specified, mass spectra with a JEOL JMS D-300 mass spectrometer at 70 eV. Pmr spectra were obtained with a Hitachi R-600 in the solvents indicated. Chemical shifts and coupling contstants were measured in ppm ($\delta$) and J (Hz) with respect to TMS.

Table I

MIC (a) (μg/ml) of 5-Substituted-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids




| Runs | No. | $R^1$ | $R^2$ | Inoculum size (b) | *S. aureus* FDA 209p | *S. pyogenes* IID S-23 | *E. coli* NIHJ JC-2 | *K. pneumoniae* | *P. rettgeri* NIH 96 | *S. marcescens* IFO 12648 | *S. sonnei* EW-33 | *S. typhi* NCTC 8393 | *P. aeruginosa* ATCC 10145 | *P. aeruginosa* NCTC 10490 | *P. aeruginosa* E-2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | H | H | × $10^8$ | >200 | >200 | 25 | 100 | 6.25 | 12.50 | 25 | 25 | >200 | >200 | >200 |
| | | | | × $10^6$ | >200 | >200 | 25 | 50 | 6.25 | 12.50 | 25 | 25 | >200 | >200 | >200 |
| 2 | 9a | OH | H | × $10^8$ | 200 | 200 | 25 | 50 | 3.13 | 12.50 | 12.50 | 100 | >200 | >200 | >200 |
| | | | | × $10^6$ | 100 | 200 | 25 | 25 | 3.13 | 12.50 | 12.50 | 25 | >200 | >200 | >200 |
| 3 | 23 | $NH_2$ | H | × $10^8$ | 50 | 200 | 100 | >200 | 12.50 | 50 | 100 | 50 | >200 | >200 | >200 |
| | | | | × $10^6$ | 25 | 200 | 100 | 200 | 12.50 | 50 | 50 | 6.25 | >200 | >200 | >200 |
| 4 | 24 | $NHC_2H_5$ | H | × $10^8$ | 50 | 100 | 100 | 200 | 6.25 | >200 | 50 | 25 | >200 | >200 | >200 |
| | | | | × $10^6$ | 25 | 50 | 100 | 100 | 3.13 | >200 | 50 | 25 | >200 | >200 | >200 |
| 5 | 8a | $OC_2H_5$ | H | × $10^8$ | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 |
| | | | | × $10^6$ | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 |
| 6 | | H | $CH_3$ | × $10^8$ | 12.50 | 200 | 1.56 | 3.13 | ≤0.39 | 1.56 | 1.56 | 0.78 | 100 | 100 | 100 |
| | | | | × $10^6$ | 6.25 | 100 | 1.56 | 3.13 | ≤0.39 | 1.56 | 1.56 | ≤0.39 | 100 | 100 | 50 |
| 7 | 9b | OH | $CH_3$ | × $10^8$ | 6.25 | 200 | 3.13 | 3.13 | 0.78 | 3.13 | 1.56 | 1.56 | 100 | >200 | 100 |
| | | | | × $10^6$ | 6.25 | 100 | 3.13 | 1.56 | ≤0.39 | 3.13 | 1.56 | 1.56 | 100 | 100 | 100 |
| 8 | 8b | $OC_2H_5$ | $CH_3$ | × $10^8$ | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 |
| | | | | × $10^6$ | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 |
| 9 | | H | $OCH_3$ | × $10^8$ | 6.25 | >50 | 3.13 | 3.13 | 0.78 | 1.56 | 1.56 | 0.78 | >50 | >50 | >50 |
| | | | | × $10^6$ | 6.25 | >50 | 1.56 | 3.13 | ≤0.39 | 1.56 | 1.56 | ≤0.39 | >50 | >50 | >50 |
| 10 | 14 | OH | $OCH_3$ | × $10^8$ | 3.13 | 200 | 3.13 | 3.13 | ≤0.39 | 1.56 | 1.56 | 0.78 | 200 | >200 | >200 |
| | | | | × $10^6$ | 3.13 | 200 | 3.13 | 3.13 | ≤0.39 | 1.56 | 1.56 | 0.78 | 100 | 100 | 100 |
| 11 | 13 | $OCH_3$ | $OCH_3$ | × $10^8$ | >50 | >50 | >50 | >50 | 6.25 | >50 | >50 | >50 | >50 | >50 | >50 |
| | | | | × $10^6$ | >50 | >50 | >50 | >50 | 3.13 | >50 | >50 | >50 | >50 | >50 | >50 |
| 12 | | Oxolinic Acid | | × $10^8$ | 0.78 | 50 | ≤0.10 | 0.39 | ≤0.10 | 0.20 | ≤0.10 | ≤0.10 | 6.25 | 6.25 | 6.25 |
| | | | | × $10^6$ | 0.78 | 25 | ≤0.10 | 0.20 | ≤0.10 | 0.20 | ≤0.10 | ≤0.10 | 6.25 | 6.25 | 6.25 |
| 13 | | 5-Aminooxolinic Acid | | × $10^8$ | 0.78 | 50 | ≤0.39 | ≤0.39 | ≤0.39 | ≤0.39 | ≤0.39 | ≤0.39 | 12.50 | 12.50 | 12.50 |
| | | | | × $10^6$ | ≤0.39 | 25 | ≤0.39 | ≤0.39 | ≤0.39 | ≤0.39 | ≤0.39 | ≤0.39 | 12.50 | 12.50 | 12.50 |
| 14 | | Nalidixic Acid | | × $10^8$ | 12.50 | 200 | 1.56 | 1.56 | 0.39 | 1.56 | 1.56 | 0.78 | 100 | 100 | 100 |
| | | | | × $10^6$ | 12.5 | 200 | 1.56 | 1.56 | 0.20 | 1.56 | 0.78 | 0.39 | 50 | 50 | 50 |

(a) Tests were performed by a heart in fusion agar dilution-streak method. (b) Potency data are in cells per milliliter.

Condensation of β-Aminovinylketones **2a,b** with EMME. Diethyl *N*-(3-Keto-1-cyclohexen-1-yl)aminomethylenemalonate (**3a**).

A mixture of 3-amino-2-cyclohexen-1-one (**2a**) (3 g) and EMME (6.4 g) was heated at 130° for 4 hours with stirring. After concentration of the mixture under reduced pressure, the resultant oil was purified by column chromatography on silica gel with ethyl acetate as an eluting solvent to give 3.65 g (49%) of **3a** as a syrup; pmr (deuteriochloroform): δ 1.31 (t, 3H, J 7, $OCH_2CH_3$), 1.36 (t, 3H, J 7, $OCH_2CH_3$), 2.0-2.7 (m, 6H, $CH_2$ × 3), 4.19 (q, 2H, J 7, $OCH_2CH_3$), 4.26 (q, 2H, J 7, $OCH_2CH_3$), 5.72 (s, 1H, COCH=), 8.14 (d, 1H, J 13, NHCH=), and 10.53 (bd, 1H, J 13, NHCH=); ir: ν 1710, 1660, 1610, and 1590 $cm^{-1}$.

Exact mass calcd. for $C_{14}H_{19}NO_5$: 281.1264. Found: 281.1265.

Diethyl *N*-(3-Keto-5-methyl-1-cyclohexen-1-yl)aminomethylenemalonate (**3b**).

A mixture of 3-amino-5-methyl-2-cyclohexen-1-one (**2b**) (1.0 g) and EMME (1.7 g) was heated at 120-130° for 5 hours with stirring. The resultant oil was purified in the same manner as described above to give 1.66 g (70%) of **3b** as a syrup; pmr (deuteriochloroform): δ 1.00-1.67 (m, 9H, $CH_3$ × 3), 1.81-2.66 (m, 5H, CH and $CH_2$ × 2), 4.25 (q, 2H, J 7, $OCH_2CH_3$), 4.30 (q, 2H, J 7, $OCH_2CH_3$), 5.73 (s, 1H, COCH=), 8.19 (d, 1H, J 13, NHCH=), and 10.76 (bd, 1H, J 13, NHCH=); ir: ν 1705, 1650, 1610, and 1590 $cm^{-1}$; ms: m/e 295 ($M^+$).

Exact mass calcd. for $C_{15}H_{21}NO_5$: 295.1417. Found: 295.1415.

Thermal Cyclization of Malonates (**3a,b**). Ethyl 4-Hydroxy-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**4a**).

The malonate **3a** (6.78 g) was added to diphenylether (42 ml) and the mixture was refluxed for 15 minutes. After cooling, *n*-hexane (80 ml) was added. The insoluble material was isolated by filtration and recrystallized from methanol to give 5.1 g (88%) of **4a**, mp 170°; pmr (deuteriochloroform): δ 1.40 (t, 3H, J 7, $OCH_2CH_3$), 2.0-3.3 (m, 6H, $CH_2$ × 3), 4.42 (q, 2H, J 7, $OCH_2CH_3$), 8.91 (s, 1H, NCH=), and 13.7 (bs, 1H, OH); ir: ν 1720, 1670, 1620, 1600, and 1550 $cm^{-1}$; uv: λ 220, 257, and 302 nm. *Anal.* Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 6.01. Found: C, 61.05; H, 5.48; N, 5.96.

Ethyl 4-Hydroxy-7-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**4b**).

A mixture of **3b** (1.47 g) and diphenylether (10 ml) was refluxed for 15 minutes. The solid was isolated in the same manner as described above and recrystallized from chloroform to give 1.10 g (88%) of **4b**, mp 217-219°; pmr (deuteriochloroform): δ 1.19 (d, 3H, J 5, $CH_3CH$), 1.39 (t, 3H, J 7, $OCH_2CH_3$), 2.08-3.28 (m, 5H, CH and $CH_2$ × 2), 4.41 (q, 2H, J 7, $OCH_2CH_3$), 8.94 (s, 1H, N=CH-), and 13.61 (s, 1H, OH); ir: ν 1715, 1640, and 1600 $cm^{-1}$; uv: λ 215, 245, and 300 nm.

*Anal.* Calcd. for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.08; N, 5.62. Found: C, 62.51; H, 5.98; N, 5.57.

Aromatization of **4a,b**. Ethyl 1,4-Dihydro-5-hydroxy-4-oxo-3-quinolinecarboxylate (**5a**).

To a solution of **4a** (5 g) in ethanol (220 ml), iodine (15 g) was added. The mixture was refluxed for 17 hours and concentrated under reduced pressure. The resultant solid was washed with ethyl acetate, water, and acetone, and recrystallized from *N,N*-dimethylformamide to give 3.06 g (62%) of **5a**, mp 294-296°; ir (tablet): ν 1690, 1625, and 1560 $cm^{-1}$; uv: λ 225, 258, and 322 nm; ms: m/e 233 ($M^+$).

Exact mass calcd. for $C_{12}H_{11}NO_4$: 233.0688. Found: 233.0689.

Ethyl 1,4-Dihydro-5-hydroxy-7-methyl-4-oxo-3-quinolinecarboxylate (**5b**).

A mixture of **4b** (500 mg) and iodine (1.5 g) in ethanol (20 ml) was refluxed for 13 hours. The solid (423 mg) isolated in the same manner as described above contained **5b** and a small amount of ethyl 1,4-dihydro-5-hydroxy-6 or 8-iodo-7-methyl-4-oxo-3-quinolinecarboxylate. It could not be separated because of instability against solvents and was used for the next step without further purification; ir (tablet): ν 1685, 1605, and 1555 $cm^{-1}$; ms: m/e 373, 248 ($M^+$).

Ethylation of **5a,b** *via* Their Thallium(I) Salts. Ethyl 1,4-Dihydro-5-ethoxy-4-oxo-3-quinolinecarboxylate (**6a**).

To a solution of **5a** (350 mg) in ethanol (5 ml), a solution of thallium(I) ethoxide (412 mg) in ethanol (1 ml) was added dropwise. The thallium(I) salt precipitated immediately, and stirring was continued for 2 hours at room temperature. The mixture was concentrated under reduced pressure. A stirred suspension of the residual salt and ethyl iodide (5 ml) was refluxed for 2 hours. The precipitated thallium(I) iodide was filtered off and washed with chloroform (5 ml). The combined filtrate was evaporated under reduced pressure to give a solid, which was subjected to column chromatography on silica gel with chloroform-methanol (30:1) as eluting solvents to give 255 mg (65%) of **6a**. Analytical sample was obtained by recrystallization from chloroform-*n*-hexane, mp 126°; pmr (deuteriochloroform): δ 1.45 (t, 3H, J 7, $CH_2CH_3$), 1.58 (t, 3H, J 7, $CH_2CH_3$) 4.25 (q, 2H, J 7, $CH_2CH_3$), 4.45 (q, 2H, J 7, $CH_2CH_3$), 6.7-7.7 (m, 3H, ArH), 8.53 (s, 1H, N=CH-), and 14.55 (s, 1H, NH); ir: ν 1720, 1690, 1630, and 1580 $cm^{-1}$; uv: λ 225, 264, and 325 nm; ms: m/e 261 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.13; H, 5.70; N, 5.48.

Ethyl 1,4-Dihydro-5-ethoxy-1-ethyl-4-oxo-3-quinolinecarboxylate (**7a**). a) Prepared from **5a**.

To a solution of **5a** (100 mg) in ethanol (4 ml), a solution of thallium(I) ethoxide (240 mg) in ethanol (1 ml) was added. The mixture was stirred at room temperature for 4 hours and concentrated under reduced pressure. A stirred suspension of the resultant salt and ethyl iodide (4 ml) was warmed at 70-80° for 4 hours. The precipitated thallium(I) iodide was filtered off and washed with chloroform. The filtrate was evaporated under reduced pressure to give a solid, which was subjected to column chromatography on silica gel with ethyl acetate-ethanol (3:1) as eluting solvents to give 85 mg (68%) of **7a**. Analytical sample was obtained by recrystallization from chloroform-ethyl acetate, mp 159°; pmr (deuteriochloroform): δ 1.40 (t, 3H, J 7, $CH_2CH_3$), 1.51 (t, 3H, J 7, $CH_2CH_3$), 1.56 (t, 3H, J 7, $CH_3$), 4.0-4.6 (m, 6H, $CH_2$ × 3), 6.80 (d, 1H, J 9, ArH), 6.95 (d, 1H, J 9, ArH), 7.53 (t, 1H, J 9, ArH), and 8.31 (s, 1H, NCH=); ir: ν 1725, 1680, 1630, 1600, and 1560 $cm^{-1}$; uv: λ 226, 265, and 321 nm; ms: m/e 289 ($M^+$).

*Anal.* Calcd. for $C_{16}H_{19}NO_4$: C, 66.46; H, 6.62; N, 4.84. Found: C, 66.17; H, 6.58; N, 4.82.

b) Prepared from **6a**.

To a solution of **6a** (14 mg) in methylene chloride (2 ml), thallium(I) ethoxide (15 mg) was added. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. A stirred suspension of the resultant solid and ethyl iodide (2 ml) was warmed at 60-70° for 2 hours. The precipitated thallium(I) iodide was filtered off and washed with chloroform. The filtrate was evaporated under reduced pressure to give 95 mg (96%) of **7a**, which showed one spot on tlc using a mixture of chloroform and ethanol (7:1) as a solvent.

Ethyl 1,4-Dihydro-5-ethoxy-1-ethyl-7-methyl-4-oxo-3-quinolinecarboxylate (**7b**).

To a solution of crude **5b** (247 mg) obtained from **4b** (292 mg) in ethanol (4 ml), a solution of thallium(I) ethoxide (600 mg) in ethanol (1 ml) was added. The mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure. A stirred suspension of the resultant salt and ethyl iodide (4 ml) was warmed at 70-80° for 4 hours. The precipitated thallium(I) iodide was filtered off and washed with chloroform. The filtrate was evaporated under reduced pressure to give a solid, which was subjected to column chromatography on silica gel with ethyl acetate-methanol (20:1) as eluting solvents to give 145 mg (41% overall yield from **4b**) of **7b**, mp 120-122°; pmr (deuteriochloroform): δ 1.20-1.80 (m, 9H, $CH_2CH_3$ × 3), 2.40 (s, 3H, $ArCH_3$), 3.85-4.55 (m, 6H, $CH_2$ × 3), 6.66 (d, 1H, J 1.2, ArH), 6.73 (d, 1H, J 1.2, ArH), and 8.26 (s, 1H, NCH=); ir: ν 1720, 1675, 1625, and 1610 $cm^{-1}$; uv: λ 228, 265, and 322 nm.

*Anal.* Calcd. for $C_{17}H_{21}NO_4$: C, 67.30; H, 6.99; N, 4.62. Found: C, 66.94; H, 6.96; N, 4.50.

Alkaline Hydrolysis of **7a,b**. 1,4-Dihydro-5-ethoxy-1-ethyl-4-oxo-3-quinolinecarboxylic Acid (**8a**).

A mixture of **7a** (1.16 g) and 10% aqueous sodium hydroxide (150 ml) was heated at 90-100° for 2.5 hours. After cooling, the solution was acidified to *p*H 1-2 by addition of 10% aqueous hydrogen chloride. The resulting solid was collected by filtration and additional solid was obtained by extraction of the aqueous layer with chloroform. The combined solid was washed with a small amount of cold water and dried to give 1.04 g (99%) of **8a**. Analytical sample was obtained by recrystallization from ethanol-water, mp 209-210°; pmr (deuteriochloroform): δ 1.10 (t, 6H, J 7, $CH_2CH_3$ × 2), 4.26 (q, 2H, $CH_2CH_3$), 4.35 (q, 2H, J 7, $CH_2CH_3$), 6.98 (d, 1H, J 9, ArH), 7.12 (d, 1H, J 9, ArH), 7.72 (t, 1H, J 9, ArH), 8.75 (s, 1H, NCH=), and 15.60 (s, 1H, COOH); ir: ν 1705, 1620, and 1560 $cm^{-1}$; uv: λ 234, 264, and 325 nm; ms: m/e 261 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.80, N, 5.36. Found: C, 64.42; H, 5.69; N, 5.40.

1,4-Dihydro-5-ethoxy-1-ethyl-7-methyl-4-oxo-3-quinolinecarboxylic Acid (**8b**).

Ethyl 1,4-dihydro-5-ethoxy-1-ethyl-7-methyl-4-oxo-3-quinolinecarboxylate (**7b**) (70 mg) was hydrolyzed by the same procedure as described above by using 10% aqueous sodium hydroxide (5 ml). There was obtained 60.4 mg (95%) of **8b** which was recrystallized from ethanol to give an analytical sample, mp 263-264°; pmr (deuteriochloroform): δ 1.23-1.64 (m, 6H, $CH_2CH_3$ × 2), 2.51 (s, 3H, $ArCH_3$), 4.08-4.35 (m, 4H, $CH_2CH_3$ × 2), 6.75 (d, 1H, J 1.2, ArH), 6.89 (d, 1H, J 1.2, ArH), 8.65 (s, 1H, NCH=), and 13.54 (s, 1H, COOH); ir (tablet): ν 1680, 1610, and 1540 $cm^{-1}$; uv: λ 237, 264, and 326 nm; ms: m/e 275 ($M^+$).

*Anal.* Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.21; H, 6.22; N, 5.09.

Deethylation of **8a,b** Using Boron Tribromide in Chloroform. 1,4-Dihydro-1-ethyl-5-hydroxy-4-oxo-3-quinolinecarboxylic Acid (**9a**).

To a cooled solution of **8a** (601 mg) in chloroform (30 ml) at -50°, a solution of boron tribromide (1.73 g) in chloroform (5 ml) was added dropwise. The green colored mixture was stirred at the same temperature for 1 hour, allowed to warm to room temperature, and warmed at 40° for 24 hours. A solution of 10% aqueous sodium hydroxide (50 ml) was added to the mixture and the separated aqueous layer was acidified by addition of 10% aqueous hydrogen chloride (50 ml). The resulting solid was collected by filtration and additional solid was obtained by extraction of the aqueous layer with chloroform. There was obtained 532 mg (99%) of **9a**, which was recrystallized from ethanol-water to give an analytical sample, mp 288-289°; pmr (DMSO-$d_6$): δ 1.43 (t, 3H, J 7, $NCH_2CH_3$), 4.56 (q, 2H, J 7, $NCH_2CH_3$), 6.96 (d, 1H, J 9, ArH), 7.41 (d, 1H, J 9, ArH), 7.85 (t, 1H, J 9, ArH), 9.10 (s, 1H, NCH=), and 13.90 (s, 1H, OH); ir (tablet): ν 1730, 1635, 1615, 1560, 1490, and 1450 $cm^{-1}$; uv: λ 225, 237, 262, and 325 nm; ms: m/e 233 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.51; H, 4.63; N, 6.03.

1,4-Dihydro-1-ethyl-5-hydroxy-7-methyl-4-oxo-3-quinolinecarboxylic Acid (**9b**).

1,4-Dihydro-5-ethoxy-1-ethyl-7-methyl-4-oxo-3-quinoline carboxylic acid (**8b**) (70 mg) was deethylated by the same procedure as described above using boron tribromide (188 mg) in chloroform (5 ml). There was obtained 56 mg (91%) of **9b**, which was recrystallized from *N,N*-dimethylformamide to give an analytical sample, mp 281-283°; pmr (DMSO-$d_6$): δ 1.41 (t, 3H, J 7, $NCH_2CH_3$), 2.50 (s, 3H, $ArCH_3$), 4.51 (q, 2H, $NCH_2CH_3$), 6.74 (s, 1H, ArH), 7.19 (s, 1H, ArH), 8.98 (s, 1H, NCH=), 12.91 (bs, 1H, OH), and 13.60 (bs, 1H, OH); ir (tablet): ν 1720, 1635, 1610, 1555, and 1440 $cm^{-1}$; uv: λ 223, 240, 264, and 324 nm; ms: m/e 247 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.90; H, 5.70; N, 5.43.

Diethyl 3,5-Dimethoxyanilinomethylenemalonate (**10**).

A mixture of 3,5-dimethoxyaniline (3 g) and EMME (4.4 g) was heated at 130° for 30 minutes with stirring. After concentration of the mixture under reduced pressure, the residual solid was recrystallized from ethanol to give 3.3 g (51%) of **10**, mp 99-100°; pmr (deuteriochloroform): δ 1.30 (t, 3H, J 7, $CH_2CH_3$), 1.36 (t, 3H, J 7, $CH_2CH_3$), 3.78 (s, 6H, $OCH_3$ × 2), 4.23 (q, 2H, J 7, $CH_2CH_3$), 4.30 (q, 2H, J 7, $CH_2CH_3$), 6.25 (s, 3H, ArH), and 8.44 (s, 1H, NCH=); ir: ν 1690, 1650, and 1590 $cm^{-1}$.

*Anal.* Calcd. for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.30; H, 6.59; N, 4.35.

Ethyl 1,4-Dihydro-5,7-dimethoxy-4-oxo-3-quinolinecarboxylate (**11**).

The malonate **10** (1 g) was added to diphenyl ether (7 ml) and the mixture was refluxed for 15 minutes. After cooling, *n*-hexane (14 ml) was added. The insoluble material was isolated by filtraiton, washed with *n*-hexane, and dried under reduced pressure to give 601 mg (72%) or crude **11**, which was recrystallized from *N,N*-dimethylformamide to give an analytical sample, mp 254-255°; ir: ν 1690, 1610, 1555, and 1535 $cm^{-1}$; uv: λ 227, 257, and 313 nm.

*Anal.* Calcd. for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60,61; H, 5.40; N, 5.22.

Ethyl 1,4-Dihydro-1-ethyl-5,7-dimethoxy-4-oxo-3-quinolinecarboxylate (**12**).

To a solution of **11** (500 mg) in ethanol (6 ml), a solution of thallium(I) ethoxide (540 mg) in ethanol (2 ml) was added dropwise. The mixture was stirred at room temperature for 2 hours and cencentrated under reduced pressure. A stirred suspension of the residual solid and ethyl iodide (6 ml) was refluxed for 4 hours. The precipitated thallium(I) iodide was filtered off and washed with chloroform (5 ml). The filtrate was concentrated under reduced pressure to give a solid, which was subjected to column chromatography on silica gel with ethyl acetate as an eluting solvent to give 424 mg (77%) of **12**, mp 124-127°; pmr (deuteriochloroform): δ 1.25 (t, 3H, J 7, $CH_2CH_3$), 1.39 (t, 3H, J 7, $CH_2CH_3$), 3.92 (s, 6H, $OCH_3$ × 2), 4.24 (q, 2H, J 7, $CH_2CH_3$), 4.38 (q, 2H, J 7, $CH_2CH_3$), 6.38 (s, 2H, ArH), 8.24 (s, 1H, NCH=); ir: ν 1720, 1675, 1630, and 1610 $cm^{-1}$; uv: λ 237, 262, and 317 nm.

*Anal.* Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.78; H, 6.07; N, 4.53.

1,4-Dihydro-1-ethyl-5,7-dimethoxy-4-oxo-3-quinolinecarboxylic Acid (**13**).

A mixture of **12** (398 mg) and 10% aqueous sodium hydroxide (15 ml) was heated at 90-100° for 2 hours. After cooling, the solution was acidified to *p*H 1-2 by addition of 10% aqueous hydrogen chloride. The resulting solid was collected by filtration and recrystallized from ethanol to give 258 mg (75%) of **13**, mp 247-248° (lit (10) 247-248°); pmr (DMSO-$d_6$): δ 1.39 (t, 3H, J 7, $NCH_2CH_3$), 3.89 (s, 3H, 7-$OCH_3$), 3.97 (s, 3H, 5-$OCH_3$), 4.49 (q, 2H, J 7, $NCH_2CH_3$), 6.67 (d, 1H, J 2, ArH), 6.79 (d, 1H, J 2, ArH), 8.80 (s, 1H, NCH=), and 16.15 (s, 1H, COOH); ir: ν 1690, 1620, 1550, 1535, and 1450 $cm^{-1}$; uv: λ 242, 263, and 320 nm.

*Anal.* Calcd. for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.78; H, 5.44; N, 5.25.

1,4-Dihydro-1-ethyl-5-hydroxy-7-methoxy-4-oxo-3-quinolinecarboxylic Acid (**14**).

To a cooled solution of **13** (70 mg) in chloroform (4 ml) at -78°, a solution of boron tribromide (190 mg) in chloroform (1 ml) was added dropwise. The green colored mixture was allowed to warm at room temperature and warmed at 40° for 2 days. A solution of 10% aqueous sodium hydroxide (5 ml) was added to the mixture and the separated aqueous layer was acidified to *p*H 1-2 by addition of 10% aqueous hydrogen chloride (3 ml) to give fine powder. After centrifuging the solid was collected by filtration under reduced pressure and recrystallized from ethanol-chloroform to give 14 mg (21%) of pure **14**, mp 245-247°; pmr (DMSO-$d_6$): δ 1.38 (t, 3H, J 7, $CH_2CH_3$), 3.92 (s, 3H, 7-$OCH_3$), 4.48 (q, 2H, J 7, $CH_2CH_3$), 6.54 (d, 1H, J 2, ArH), 6.75 (d, 1H, J 2, ArH), 8.93 (s, 1H, NCH=), 10.88 (s, 1H, OH), and 13.19 (s, 1H, OH); ir: ν 1710, 1640, 1560, and 1440; uv: λ 223, 261, and 323 nm.

*Anal.* Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98, N, 5.32. Found: C, 59.19; H,4.62; N, 5.35.

Ethyl 4-Hydroxy-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate Oxime (**15**).

A solution of hydroxylamine hydrochloride (0.36 g) and sodium acetate (0.42 g) in water (10 ml) was added to a solution of **4a** (1.0 g) in ethanol-water (1:1, 10 ml). The mixture was refluxed for 1 hour and the precipitated crystal was collected by filtration and washed with water. Recrystallization from ethanol gave 957 mg (90%) of **15**, mp 245-248°; pmr (DMSO-$d_6$): δ 1.30 (t, 3H, J 7, $OCH_2CH_3$), 1.60-2.15 (m, 2H, $CH_2$), 2.50 (s, 2H, $CH_2$), 2.7-2.9 (m, 2H, $CH_2$), 4.28 (q, 2H, J 7, $OCH_2CH_3$), 8.54 (s, 1H, NCH=), 11.71 (bs, 1H, OH), and 13.11 (bs, 1H, OH); ir (tablet): ν 1695, 1635, 1530, and 1170 $cm^{-1}$; uv: λ 228 and 340 nm.

*Anal.* Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.55; H, 5.57; N, 10.91.

Cyclization of **15** into Isoxazole **16**.

To a solution of the oxime **15** (2 g) and pyridine (950 mg) in chloroform (55 ml), a solution of ethyl chloroformate (1.3 g) in chloroform (55 ml), a solution of ethyl chloroformate (1.3 g) in chloroform (28 ml) was added dropwise over 30 minutes. The mixture was allowed to stand at room temperature for 2 days. The chloroform layer was washed with water (30 ml × 3), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with ethyl acetate as an eluting solvent to give 1.67 g (90%) of **16** as a crystal, mp 102°; pmr (deuteriochloroform): δ 1.47 (t, 3H, J 7, $OCH_2CH_3$), 1.90-2.70 (m, 2H, $CH_2$), 2.95-3.40 (s, 4H, $CH_2$ × 2), 4.50 (q, 2H, J 7, $OCH_2CH_3$), and 9.14 (s, 1H, N=CH-); ir: ν 1715, 1640, 1605, and 1125 $cm^{-1}$; uv: λ 212 and 250 nm.

*Anal.* Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.95; H, 5.11; N, 12.00.

Aromatization of **16** Using Iodine-Potassium Iodide. Ethyl 5-Amino-1,4-dihydro-6 or 8-iodo-4-oxo-3-quinolinecarboxylate (**17**).

A suspension of **16** (800 mg), *p*-toluenesulfonic acid (13 mg), iodine (877 mg), and potassium iodide (1.7 g) in ethanol (18 ml) was refluxed for 1 hour. After cooling, the resultant crystal was collected by filtration, washed with water, ethanol, and aqueous sodium thiosulfate, and dried to give 608 mg (50%) of **17**. Analytical sample was obtained by recrystallization from *N,N*-dimethyl formamide, mp 238° dec; pmr (DMSO-$d_6$): δ 1.28 (t, 3H, J 7, $CH_2CH_3$), 4.20 (q, 2H, J 7, $CH_2CH_3$), 6.49 (d, 1H, J 9, ArH), 7.68 (d, 1H, J 9, ArH), 7.80 (bs, 2H, $NH_2$), and 8.35 (s, 1H, NCH=); ir (tablet): ν 1690, 1610, 1530, and 1500 $cm^{-1}$; uv: λ 224 and 350 nm; ms: m/e 358 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{11}IN_2O_3$: C, 40.26; H, 3.10; N, 7.82. Found: C, 40.37; H, 3.14; N, 7.29.

Ethylation of **17** *via* Its Thallium(I) Salt. Ethyl 5-Amino-1,4-dihydro-1-ethyl-6- or 8-iodo-4-oxo-3-quinoline carboxylate (**18**) and Ethyl 1,4-Dihydro-1-ethyl-5-ethylamino-6- or 8-iodo-4-oxo-3-quinolinecarboxylate (**19**).

To a solution of **17** (1.5 g) in ethanol (20 ml), a solution of thallium(I) ethoxide (1.25 g) in ethanol (2 ml) was added. The mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure. A stirred suspension of the residual salt and ethyl iodide (15 ml) was warmed at 60-70° for 4 hours. The precipitated thallium(I) iodide was filtered off and washed with acetone. The filtrate was concentrated under reduced pressure to give a residue, which was subjected to column chromatography on silica gel with ethyl acetate as an eluting solvent to give 142 mg (8%) of **19** as a syrup; pmr (deuteriochloroform): δ 0.97-1.70 (m, 9H, $CH_2CH_3$ × 3), 3.20-4.60 (m, 6H, $CH_2CH_3$ × 3), 6.76 (d, 1H, J 9, ArH), 8.32 (d, 1H, J 9, ArH), and 8.65 (s, 1H, NCH=); ms: m/e 414 ($M^+$).

Further elution with the same solvent gave 591 mg (37%) of **18**. Analytical sample was obtained by recrystallization from ethyl acetate, mp 179-180°; pmr (deuteriochloroform): δ 1.42 (t, 3H, J 7, $CH_2CH_3$), 1.49 (t, 3H, J 7, $CH_2CH_3$), 4.10 (q, 2H, J 7, $CH_2CH_3$), 4.38 (q, 2H, J 7, $CH_2CH_3$), 6.29 (d, 1H, J 9, ArH), 7.73 (d, 1H, J 9, ArH), and 8.30 (s, 1H, NCH=); ir: ν 1720, 1630, and 1580 $cm^{-1}$; uv: λ 241, 279, and 355 nm; ms: m/e 386 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{15}IN_2O_3$: C, 43.54; H, 3.92; N, 7.25. Found: C, 43.43; H, 3.82; N, 7.35.

Deiodination of a Mixture of **18** and **19** by Catalytic Hydrogenation of Ethyl 5-Amino-1,4-dihydro-1-ethyl-4-oxo-3-quinolinecarobxylate (**20**) and Ethyl 1,4-Dihydro-1-ethyl-5-ethylamino-4-oxo-3-quinoline carboxylate (**21**).

A mixture of **18** and **19** (650 mg) obtained by ethylation of **17** (1.34 g) *via* its thallium(I) salt was submitted to the standard catalytic hydrogenolysis over 5% palladium-carbon (100 mg) in ethanol (40 ml) in the presence of triethylamine (2 ml) at 40° and 3 atmospheres hydrogen pressure for 10 hours. After removal of palladium-carbon by filtration, the filtrate was concentrated under reduced pressure. The residue was partitioned between chloroform (30 ml) and saturated aqueous sodium bicarbonate (10 ml). The organic layer was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue, which was subjected to column chromatography on silica gel with ethyl acetate-ethanol (50:1) as eluting solvents to give 68 mg (14%) of **21** as a syrup. This was used for the next step without further purification; pmr (deuteriochloform): δ 1.20-1.63 (m, 9H, $CH_2CH_3$ × 3), 3.00-3.45 (m, 1H, $C_5$-$NHC_2H_5$), 4.07 (q, 2H, J 7, $CH_2CH_3$), 4.36 (q, 2H, J 7, $CH_2CH_3$), 6.35 (d, 2H, J 9, ArH), 7.35 (t, 1H, J 9, ArH), and 10.3 (bs, 1H, NH); ir: ν 1715, 1690, 1630, and 1575 $cm^{-1}$.

Further elution with ethyl acetate-ethanol (4:1) as eluting solvents gave 276 mg (63%) of **20** as a crystalline solid which was recrystallized from ethyl acetate-ethanol to give an analytical sample, mp 200-201°; pmr (deuteriochloroform): δ 1.38 (t, 3H, J 7, $CH_2CH_3$), 1.47 (t, 3H, J 7, $CH_2CH_3$), 4.08 (q, 2H, J 7, $CH_2CH_3$), 4.37 (q, 2H, J 7, $CH_2CH_3$), 6.44 (d, 2H, J 9, ArH), 7.26 (t, 1H, J 9, ArH), 7.45 (bs, 2H, $NH_2$), and 8.32 (s, 1H, NCH=); ir: ν 1705, 1630, and 1575 $cm^{-1}$; uv: λ 227 277, and 350 nm; ms: m/e 260 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.13; H, 6.20; N, 10.58.

Alkaline Hydrolysis of the Ester (**20**, **21**, and **17**). 5-Amino-1,4-dihydro-1-ethyl-4-oxo-3-quinolinecarboxylic Acid (**22**).

A mixture of **20** (78 mg) and 10% aqueous sodium hydroxide (15 ml) was heated at 80-90° for 2 hours. After cooling, the solution was acidified to *p*H 5-6 by addition of 10% aqueous hydrogen chloride. The resultant solid was collected by filtration and additional solid was obtained by extraction of the aqueous layer with chloroform. The combined solid was washed with a small amount of cold water and dried to give 68 mg (98%) of **22**. An analytical sample was obtained by recrystallization from chloroform, mp 279-281°; pmr (DMSO-$d_6$): δ 1.38 (t, 3H, J 7, $CH_2CH_3$), 4.48 (q, 2H, J 7, $CH_2CH_3$), 6.66 (d, 1H, J 9, ArH), 6.80 (d, 1H, J 9, ArH), 7.49 (t, 1H, J 9, ArH), 7.65 (bs, 2H, $NH_2$), 8.84 (s, 1H, NCH=), and 12.82 (s, 1H, COOH); ir (tablet): ν 1690, 1625, 1600, and 1440 $cm^{-1}$; uv: λ 233, 274, and 355 nm; ms: m/e 232 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.95; H, 5.06; N, 12.03.

1,4-Dihydro-1-ethyl-5-ethylamino-4-oxo-3-quinolinecarboxylic Acid (**23**).

Ethyl 1,4-dihydro-1-ethyl-5-ethylamino-4-oxo-3-quinolinecarboxylate (**21**) (58 mg) was hydrolyzed by the same procedure as described above by using 10% aqueous sodium hydroxyide (10 ml). There was obtained 47 mg (90%) of **23**, which was recrystallized from ethanol to give an analytical sample, mp 188-191°; pmr (deuteriochloroform): δ 1.34 (t, 3H, J 7, $CH_2CH_3$), 1.54 (t, 3H, J 7, $CH_2CH_3$), 3.05-3.48 (m, 2H, $NCH_2$), 4.25 (q, 2H, J 7, $CH_2CH_3$), 6.50 (d, 1H, J 9, ArH), 6.57 (d, 1H, J 9, ArH), 7.49 (t, 1H, J 9, ArH), 8.60 (s, 1H, NCH=), 9.60 (bs, 1H, NH), and 15.0 (bs, 1H, COOH); ir: ν 1710, 1620, and 1450 $cm^{-1}$; uv: λ 230, 277, and 378 nm.

*Anal.* Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.69; H, 6.10; N, 10.59.

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