Synthesis of 1,4-Dihydro-2-methyl-4-oxo-3-quinolineglyoxylic Acid and Related Compounds

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The synthesis of 1,4-dihydro-1-methoxy or ethyl -2-methyl-4-oxo-3-quinolineglyoxylic acid derivatives are described. α-Acetoxy-1,4-dihydro-1-hydroxy-2-methyl-4-oxo-3-quinolineacetic acid esters (**7a, 7b**), which are key intermediates, were prepared by catalytic hydrogenation of 2-acetoxy-3-acetyl-4-hydroxy-4-(2-nitrophenyl)crotonic acid lactone (**6**) in methanol or ethanol.

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The synthesis of active analogues of nalidixic acid (1) which is a potent chemotherapeutic agent used mainly in the treatment of urinary tract infections with gram-positive pathogens has extensively been studied (2). The common features of these compounds contain the 1,4-dihydro-1-ethyl-4-oxo-3-pyridinecarboxylic acid moiety. Miloxacin (3), which has the 1,4-dihydro-1-methoxy-4-oxo-3-pyridinecarboxylic acid moiety, possesses activity against both gram-negative and gram-positive bacteria. Recently, Nishimura, *et al.*, reported the synthesis and antibacterial activity of 8-ethyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-glyoxylic acid derivatives (4). Smith and co-worker (5) also reported the synthesis of a series of 2-alkyl-4-quinolone, some of which are naturally occurring alkaloids from the family *Rutaceae* (6). In these connections, we would like to report the convenient synthesis of the 1,4-dihydro-2-methyl-4-oxo-3-quinolineglyoxylic acid derivatives.

Previously, we reported (7) the reductive cyclization of 3-acetyl-2,4-dihydroxy-4-(2-nitrophenyl)crotonic acid lactone (**1**), prepared by condensation of 2-nitrobenzaldehyde with ethyl 2,4-dioxopentanoate (8), in the presence of 5% palladium-carbon gave α-hydroxy-2-methyl-3-quinolineacetic acid 1-oxide (**2**). On the other hand, catalytic hydrogenation of the methyl ether (3), which was obtained by treatment of **1** with diazomethane, over 5% palladium-carbon in methanol gave methyl 1,4-dihydro-1-hydroxy-α-methoxy-2-methyl-4-oxo-3-quinolineacetate (**4**).

In order to introduce the $COCO_2R$ (R = H, or alkyl) at the C(3)-position of compound **4**, we examined the following modifications. Catalytic hydrogenation of the benzyl ether (**5**), prepared by reaction of **1** with phenyldiazomethane (9), expecting to obtain **9** resulted in the formation of **2**, unfortunately. Thus, treatment of **1** with acetic anhydride in acetic acid gave the acetate (**6**), which was then catalytically hydrogenated over 5% palladium-carbon in methanol or ethanol to give methyl or ethyl α-acetoxy-1,4-dihydro-1-hydroxy-2-methyl-4-oxo-3-quinolineacetates (**7a** and **7b**) in good yields. Treatment of **7a** with dimethyl sulfate in acetone gave the *N*-methoxyquinolone (**8**) in 83% yield. Acid-catalyzed hydrolysis of **8** gave **9** which was then oxidized with manganese dioxide in dichloromethane to yield methyl 1,4-dihydro-1-methoxy-2-methyl-4-oxo-3-quinolineglyoxylate (**10**), quantitatively. To obtain the corresponding carboxylic acid (**15**), one of the target compound, of **10**, base-catalyzed hydrolysis of **10** was at-

Chart 1

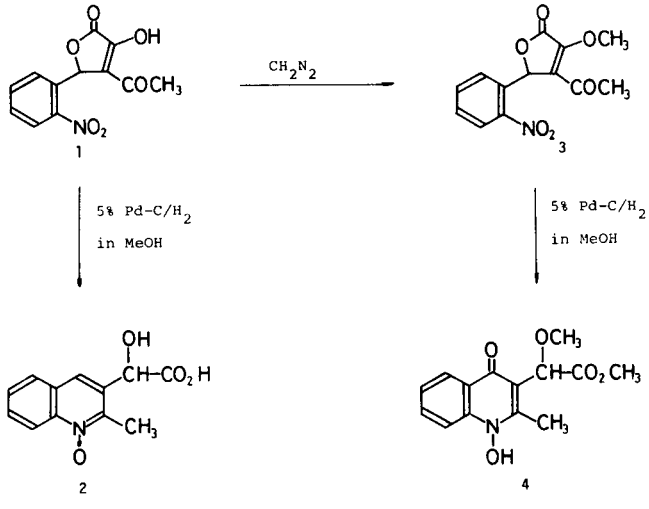


Chart 2

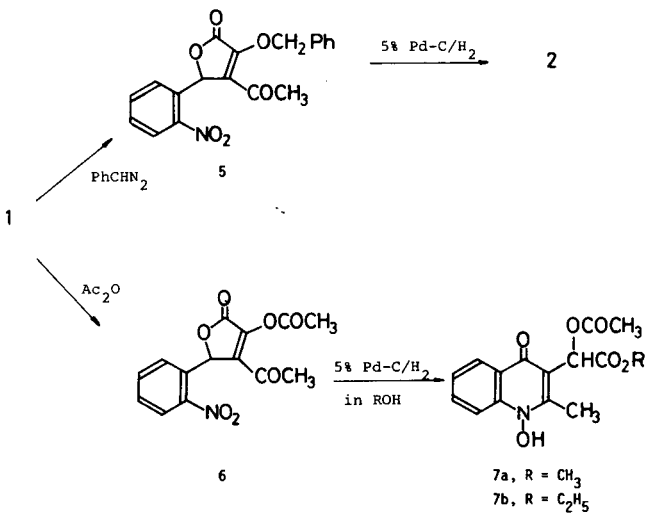


Chart 3

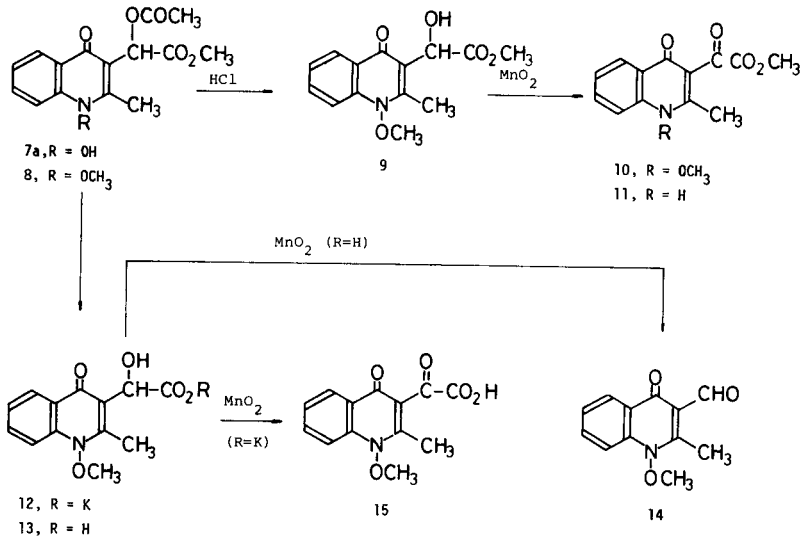
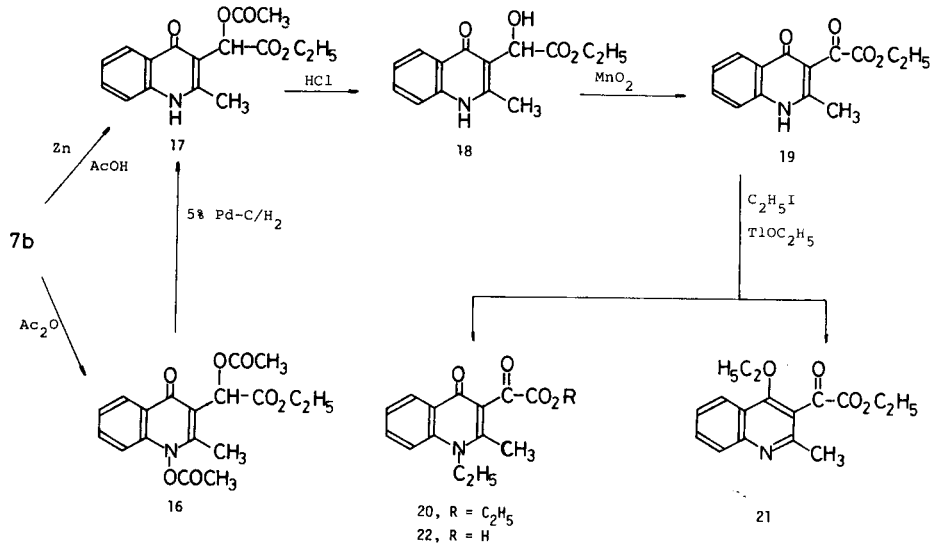


Chart 4



tempted but gave none of the desired product, with only the demethoxy derivative (**11**) being isolated. On the other hand, by treatment of **8** with potassium hydroxide in ethanol, potassium salt (**12**) was isolated. Manganese dioxide oxidation of the carboxylic acid (**13**), however gave the 3-formyl derivative (**14**) formed by the oxidative decarbonylation. Thus, manganese dioxide oxidation of the potassium salt (**12**) in water followed by acidification afforded successfully 1,4-dihydro-1-methoxy-2-methyl-4-oxo-3-quinolineglyoxylic acid (**15**) in moderate yield.

Next, synthesis of the *N*-ethyl derivative (22) was attempted. Reduction of **7b** with zinc powder in acetic acid gave the 1-deoxy derivative (**17**), which was alternatively obtained by the catalytic hydrogenation of the acetate (**16**). Partial acid-catalyzed hydrolysis of **17** gave **18** which was subsequently oxidized with manganese dioxide to yield ethyl 1,4-dihydro-2-methyl-4-oxo-3-quinolineglyoxylate (**19**). Tamura (10) has reported a useful method for the regioselective *N*-alkylation of ethyl 1,4-dihydro-4-oxopyridine-3-carboxylates by thallium(I) ethoxide and alkyl halides. According to this method, treatment of **19** with a slight excess of thallium(I) ethoxide in ethanol at room temperature afforded the thallium(I) salt, whose proton magnetic resonance (pmr) spectrum in deuteriodimethylsulfoxide showed the disappearance of the $CO_2CH_2CH_3$ protons, unexpectedly. Heating of a mixture of the

thallium(I) salt and a large excess of ethyl iodide at 70° for 6 hours followed by silica gel column chromatographical separation gave a mixture of the desired *N*-ethylated product (**20**) (12% yield) and the *O*-ethylated product (**21**) (11% yield) together with 11% of **19**. The structural assignments of **20** and **21** are mainly based on microanalyses and ultraviolet (uv) spectral data. Thus, the uv spectrum of **20** (λ 222, 268, and 318 nm) are closely similar to that of **19** (λ 218, 266, and 310 nm). Upon acid or base-catalyzed hydrolyses of **20**, the desired carboxylic acid (**22**) could not be obtained.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra (potassium bromide unless otherwise noted) were recorded with a JASCO model IRA-1 spectrophotometer. The pmr spectra were recorded in deuteriodimethylsulfoxide (unless otherwise noted) with a Hitachi R-40 spectrometer with tetramethylsilane as an internal standard. The mass spectrum was recorded with a Hitachi RMU-7L spectrometer.

3-Acetyl-2-benzyloxy-4-hydroxy-4-(2-nitrophenyl)crotonic Acid Lactone (**5**).

A suspeniosn of 1.5 g of **1** in 40 ml of petroleum ether including an excess of phenyldiazomethane was stirred for 2 hours. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 1.25 g (62%) of **5** as colorless needles of mp 123-124°; ir: ν cm^{-1} 1780, 1670 (CO), 1640 (C=C), 1540, 1370 (NO_2); pmr: δ 2.33 (3H, s, $COCH_3$), 5.74 (2H, s, CH_2), 6.66 (1H, s, CH), 7.26-8.10 (9H, m, Ar-H).

Anal. Calcd. for $C_{19}H_{15}NO_6$: C, 64.58; H, 4.28; N, 3.96. Found: C, 64.31; H, 4.40; N, 4.09.

2-Acetoxy-3-acetyl-4-hydroxy-4-(2-nitrophenyl)crotonic Acid Lactone (**6**).

A solution of 5 g of **1** in a mixture of 30 ml of acetic acid and 30 ml of acetic anhydride was heated at 100° for 2.5 hours. After removal of the solvent by evaporation, the residue was recrystallized from ethanol to give 5.4 g (93%) of **6** as colorless needles of mp 104-105°; ir: ν cm^{-1} 1795, 1780, 1680 (CO), 1540, 1350 (NO_2); pmr (deuteriochloroform): δ 2.38 and 2.45 (each 3H, each s, $COCH_3$ and/or $OCOCH_3$), 7.10 (1H, s, CH), 7.20-8.10 (4H, m, Ar-H).

Anal. Calcd. for $C_{14}H_{11}NO_7$: C, 55.08; H, 3.63; N, 4.59. Found: C, 54.88; H, 3.41; N, 4.54.

Catalytic Hydrogenation of **5**.

A solution of 1.1 g of **5** in 100 ml of methanol was shaken with hydrogen over 0.3 g of 5% palladium-carbon for 2 hours using a Skita apparatus. The reaction mixture was filtered and concentrated *in vacuo*. The residue was recrystallized from water to give 471 mg (64%) of **2**, mp 242-243°, which was identical with an authentic sample (7) in all aspects.

Catalytic Hydrogenation of **6** in Methanol or Ethanol.

A solution of 0.01 mole of **6** in 100 ml of methanol (or ethanol) was shaken with hydrogen over 1.0 g of 5% palladium-carbon for 15 minutes using a Skita apparatus. The reaction mixture was filtered and concentrated *in vacuo*. The residue was recrystallized from an appropriate solvent, respectively.

Methyl α-Acetoxy-1,4-dihydro-1-hydroxy-2-methyl-4-oxo-3-quinolineacetate (**7a**).

Colorless needles of mp 192-193° (methanol); yield 77%; ir: ν cm^{-1} 2400-2800 (N-OH), 1750 (CO); pmr: δ 2.10 (3H, s, $OCOCH_3$), 3.63 (3H, s, CO_2CH_3), 66.66 (1H, s, CH), 7.30-8.25 (4H, m, Ar-H), 11.85 (11H, s, OH).

Anal. Calcd. for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.26; H, 4.66; N, 4.60.

Ethyl α-Acetoxy-1,4-dihydro-1-hydroxy-2-methyl-4-oxo-3-quinolineacetate (**7b**).

Colorless needles of mp 172-173° (ethyl acetate-*n*-hexane), yield, 72%; ir: ν cm^{-1} 2400-2800 (N-OH), 1750 (CO); pmr: δ 1.12 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.10 (3H, s, $OCOCH_3$), 2.51 (3H, s, CH_3), 4.12 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 6.66 (1H, s, CH), 7.30-8.24 (4H, m, Ar-H), 11.85 (1H, bs, OH).

Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.21; H, 5.31; N, 4.60.

Methyl α-Acetoxy-1,4-dihydro-1-methoxy-2-methyl-4-oxo-3-quinolineacetate (**8**).

To a solution of 2 g of **7a** and 865 mg of dimethyl sulfate in 100 ml of acetone, 1.81 g of potassium carbonate was added. The mixture was stirred under gentle refluxing for 30 minutes. The insoluble solid was filtered off and washed with acetone. The combined filtrate was evaporated under reduced pressure to give a solid, which was recrystallized from ethanol to give 1.92 g (93%) of **8** as colorless needles of mp 124-125°; ir: ν cm^{-1} 1760, 1740 (CO); pmr: δ 2.13 (3H, s, $OCOCH_3$), 2.60 (3H, s, CH_3), 3.63 (3H, s, CO_2CH_3), 4.08 (3H, s, OCH_3), 6.60 (1H, s, CH), 7.35-8.26 (4H, m, Ar-H).

Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 59.97; H, 5.31; N, 4.63.

Methyl 1,4-Dihydro-α-hydroxy-1-methoxy-2-methyl-4-oxo-3-quinolineacetate (**9**).

A mixture of 3 g of **8** and 3 ml of concentrated hydrochloric acid in 300 ml of methanol was heated at 55° for 10 hours. After removal of the solvent by evaporation, the residue was neutralized by the addition of saturated sodium bicarbonate solution. The resulting solid was collected by filtration and recrystallized from ethyl acetate to give 2.23 g (82%) of **9** as colorless needles of mp 142-143°; ir: ν cm^{-1} 3200-3400 (OH), 1760, 1620 (CO); pmr: δ 2.60 (3H, s, CH_3), 3.62 (3H, s, CO_2CH_3), 4.06 (3H, s, OCH_3), 5.60 (1H, d, J = 6 Hz, C*H*OH), 5.73 (1H, d, J = 6 Hz, CHO*H*), 7.33-8.30 (4H, m, Ar-H).

Anal. Calcd. for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.37; H, 5.31; N, 5.05.

Methyl 1,4-Dihydro-1-methoxy-2-methyl-4-oxo-3-quinolineglyoxylate (**10**).

A suspension of 0.5 g of **9** and 1.5 g of manganese dioxide in 30 ml of chloroform was stirred for 5 hours at room temperature. Manganese dioxide was filtered off and washed with chloroform. The combined filtrate was concentrated *in vacuo*. The residue was recrystallized from ethanol to give 485 mg (98%) of **10** as pale yellow needles of mp 195-196°; ir: ν cm^{-1} 1740, 1680, 1610 (CO); pmr: δ 2.86 (3H, s, CH_3), 3.80 (3H, s, CO_2CH_3), 4.14 (3H, s, OCH_3), 7.46-8.30 (4H, m, Ar-H).

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.81; H, 4.84; N, 5.08.

Treatment of **10** with Potassium Hydroxide.

A solution of 66 mg of potassium hydroxide in 2 ml of water was added to a solution of 275 mg of **10** in 50 ml of methanol, and then the mixture was allowed to stand for 10 hours. The solution was tinged with red. After removal of the solvent by evaporation, the residue was recrystallized from ethanol-water to give 85 mg (35%) of methyl 1,4-dihydro-2-methyl-4-oxo-3-quinolineglyoxylate (**11**) as pale yellow needles of mp 213-215°; ir: ν cm^{-1} 2900 (NH), 1740, 1660, 1610 (CO); pmr: δ 2.73 (3H, s, CH_3), 3.83 (3H, s, CO_2CH_3), 7.40-8.15 (4H, m, Ar-H), 12.50 (1H, bs, NH).

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.41; H, 4.38; N, 5.99.

1,4-Dihydro-α-hydroxy-1-methoxy-2-methyl-4-oxo-3-quinolineacetic Acid (**13**).

A solution of 66 mg of potassium hydroxide in 2 ml of water was added to a solution of 319 mg of **8** in 30 ml of methanol, and then the mixture was allowed to stand for 30 minutes. The solution was concentrated to

one-third of its original volume, and cooled. The resulting precipitate was collected by filtration and dried to give 302 mg (100%) of the potassium salt (**12**); ir: ν cm^{-1} 3300 (OH), 1600 (CO); pmr: δ 2.48 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 4.75 (1H, bs, OH), 5.20 (1H, s, OH), 7.25-8.26 (4H, m, Ar-H). A solution of 302 mg of **12** in 3 ml of water was acidified by the addition of 5% hydrochloric acid under ice cooling. The resulting solid was collected by filtration and dried to give 245 mg (93%) of **13**, which was recrystallized from water to give an analytical sample as colorless needles of mp 184-185°; ir: ν cm^{-1} 3400 (OH), 1700 (CO); pmr: δ 2.53 (3H, s, CH_3), 4.02 (3H, s, OCH_3), 4.40 (2H, s, CO_2H and OH), 5.39 (1H, s, CH), 7.30-8.30 (4H, m, Ar-H).

Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.17; H, 5.17; N, 5.21.

1,4-Dihydro-1-methoxy-2-methyl-4-oxo-3-quinolinecarboxaldehyde (**14**).

A suspension of 263 mg of **13** and 0.5 g of manganese dioxide in 100 ml of water was stirred overnight at 30°. The insoluble solid was collected by filtration, and then extracted with chloroform. After removal of the solvent by evaporation, the residue was recrystallized from ethanol-water to give 97 mg (45%) of **14** as pale yellow needles of mp 167-168°; ir: ν cm^{-1} 1670, 1620 (CO); pmr: δ 2.90 (3H, s, CH_3), 4.10 (3H, s, OCH_3), 7.45-8.35 (4H, m, Ar-H), 10.42 (1H, s, CHO).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.44; H, 4.88; N, 6.56.

1,4-Dihydro-1-methoxy-2-methyl-4-oxo-3-quinolineglyoxylic Acid (**15**).

A suspension of 1.47 g of **12** and 5.0 g of manganese dioxide in 10 ml of water was stirred overnight at room temperature. Manganese dioxide was filtered off and the filtrate was acidified by the addition of 5% hydrochloric acid under ice cooling. The precipitate was collected by filtration and recrystallized from ethanol to give 668 mg (53%) of **15** as colorless needles of mp 204-206°; ir: ν cm^{-1} 2800-3100 (OH), 1750, 1660, 1610 (CO); pmr: δ 2.82 (3H, s, CH_3), 4.12 (3H, s, OCH_3), 7.45-8.26 (4H, m, Ar-H).

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.55; H, 4.03; N, 5.44.

Ethyl 1,α-Diacetoxy-1,4-dihydro-2-methyl-4-oxo-3-quinolineacetate (**16**).

Three drops of pyridine were added to a solution of 5 g of **7b** in 30 ml of acetic anhdyride, and the mixture was allowed to stand for 6 hours. After removal of acetic anhydride by evaporation, the residue was dissolved in chloroform. The chloroform solution was washed with saturated sodium bicarbonate solution, water, and dried over anhydrous sodium sulfate. After removal of the solvent by evaporation, the resultant oil was purified by column chromatography on silica gel with ethyl acetate as an eluting solvent to give 5.18 g (92%) of **16** as a colorless oil; ir (chloroform): ν cm^{-1} 1790, 1750, 1730 (CO); pmr (deuteriochloroform): δ 1.15 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.10, 2.35 and 2.45 (each 3H, each s, CH_3 and/or 2 × $OCOCH_3$), 4.15 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 6.70 (1H, s, CH), 7.10-8.13 (4H, m, Ar-H); ms: m/z 345 (M^+).

Ethyl α-Acetoxy-1,4-dihydro-2-methyl-4-oxo-3-quinolineacetate (**17**).

a) Prepared from **7b**.

To a solution of 3.19 g of **7b** in 200 ml of acetic acid, 5 g of zinc powder was added in small portions under vigorous stirring. The mixture was heated at 70° for 4 hours with stirring, and cooled. The insoluble material was filtered off, and washed with acetic acid. The combined filtrate was condensed under reduced pressure to give a solid, which was recrystallized from ethyl acetate to give 2.24 g (74%) of **17** as colorless needles of mp 205-207°; ir: ν cm^{-1} 1740, 1630 (CO); pmr: δ 1.15 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.10 (3H, s, $OCOCH_3$), 2.45 (3H, s, CH_3), 4.10 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 6.55 (1H, s, CH), 7.20-8.20 (4H, m, Ar-H).

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.39; H, 5.71; N, 4.61.

b) Prepared from **16**.

A solution of 11 g of **16** in 100 ml of ethanol was shaken with hydrogen over 3.0 g of 5% palladium-carbon for 8 hours using a Skita apparatus at 40°. The reaction mixture was filtered off and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate to give 6.76 g (73%) of **17**.

Ethyl 1,4-Dihydro-α-hydroxy-2-methyl-4-oxo-3-quinolineacetate (**18**).

A mixture of 3 g of **17** and 3 ml of concentrated hydrochloric acid in 300 ml of ethanol was treated as described for the preparation of **9** to give 1.96 g (76%) of **18**, mp 200-202°, which was recrystallized from ethyl acetate; ir: ν cm^{-1} 3080-3300 (OH and NH), 1750, 1630 (CO); pmr: δ 1.15 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.45 (3H, s, CH_3), 4.10 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 5.45 (1H, s, CH), 7.20-8.10 (4H, m, Ar-H).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.54; H, 5.81; N, 5.47.

Ethyl 1,4-Dihydro-2-methyl-4-oxo-3-quinolineacetate (**19**).

A suspension of 1.3 g of **18** and 5 g of manganese dioxide in 200 ml of water was stirred at 40° for 3 days. The insoluble material was collected by filtration, and extracted with ethyl acetate. After removal of the solvent by evaporation, the residue was recrystallized from ethyl acetate to give 727 mg (64%) of **19** as colorless needles of mp 215-216°; ir: ν cm^{-1} 1740, 1650, (CO); pmr: δ 1.30 (3H, J = 7 Hz, $CO_2CH_2CH_3$), 2.70 (3H, s, CH_3), 4.25 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 7.35-8.15 (4H, m, Ar-H); uv: λ nm 218, 266, and 318.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.96; H, 5.05; N, 5.37.

Reaction of **19** with Ethyl Iodide and Thalliam(I) Ethoxide.

To a solution of 778 mg of **19** in 12 ml of ethanol, a solution of 1.792 g of thallium(I) ethoxide in 7 ml of ethanol was added. The mixture was stirred for 2 hours at room temperature. The resultant thallium(I) salt was collected by filtration, and dried. A stirred suspension of thallium(I) salt and 10 ml of ethyl iodide was refluxed for 6 hours. The precipitated thallium(I) iodide was filtered off and washed with chloroform. The combined filtrate was concentrated *in vacuo* to give an oil, which was subjected to column chromatography on silica gel. The first fraction eluted with benzene-ethyl acetate (3:1) gave 94 mg (11%) of ethyl 4-ethoxy-2-methyl-3-quinolineglyoxylate (**21**), mp 79°, which was recrystallized from *n*-hexane; ir: ν cm^{-1} 1730, 1680 (CO); pmr: (deuteriochloroform): δ 1.40 and 1.50 (each 3H, each t, J = 7 Hz, $CO_2CH_2CH_3$ and/or NCH_2CH_3), 7.40-8.20 (4H, m, Ar-H); uv: λ nm 220, 250, and 290.

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.83; H, 5.96; N, 5.02.

From the second fraction eluted with the same solvent as above, 100 mg (12%) of ethyl 1,4-dihydro-1-ethyl-2-methyl-4-oxo-3-quinolineglyoxylate (**20**) was obtained. This was recrystallized from ethanol to give an analytical sample of mp 163-164°; ir: ν cm^{-1} 1740, 1650, 1620 (CO); pmr: δ 1.20-1.50 (6H, m, $CO_2CH_2CH_3$ and NCH_2CH_3), 2.80 (3H, s, CH_3), 4.35 and 4.50 (each 2H, each q, J = 7 Hz, $CO_2CH_2CH_3$ and/or NCH_2CH_3), 7.50-8.30 (4H, m, Ar-H); uv: λ nm 222, 268, and 318.

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.94; H, 5.92; N, 5.03.

The third fraction eluted with ethyl acetate gave 88 mg (11%) of **19**, mp 215-216°, recrystallized from ethyl acetate.

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