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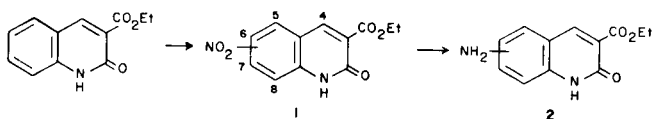
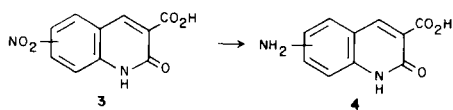
The structures of the products from the nitration of 2- and 4-oxodihydroquinolines were assigned based on Nuclear Overhauser Effects of their nmr spectra and confirmed by unambiguous synthesis.

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During the course of studies on semisynthetic penicillins [1], several 2- and 4-oxo dihydroquinolines were nitrated in our laboratory. It was imperative that their regiochemistry be clearly assigned, but analysis of the routine proton nmr spectra of the nitration products did not allow assignment. The application of Nuclear Overhauser Effect (NOE) techniques [2] on the nitration products and other synthetic derivatives allowed definitive assignment, as described below.

The synthesis of 1,2-dihydro-2-oxo-3-quinolinecarboxylic acid, ethyl ester was accomplished by condensing *o*-nitrobenzaldehyde with diethyl malonate using the method of Loudon and Wellings [3]. The product, [(2-nitrophenyl)methylene]propanedioic acid diethyl ester, was then hydrogenated over Raney Nickel to give the desired product [4]. Nitration of the reduction product with nitric and sulfuric acids gave a single mononitration product **1** based upon elemental analysis. The nmr spectrum (see Table) indicated that nitration took place at either the C6 or C7 position, based upon the coupling pattern, but the data could be interpreted to fit either isomer. Neither reduction of the nitro group to give amine **2** nor hydrolysis of the ester **1** to give the acid **3**, followed by reduction of the nitro functionality to give amine **4** clarified the structural assignment of the isomer (Scheme 1).

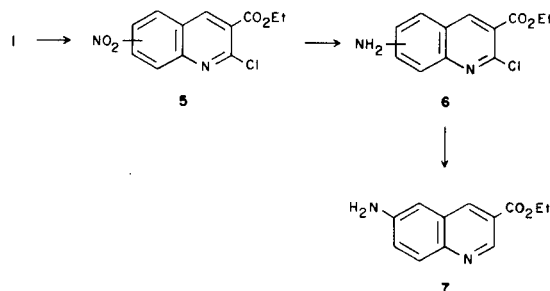
Scheme 1



Two synthetic routes were initiated to establish the structure of the nitration product **1**. The first approach (Scheme 2) involved the chlorination of **1**, followed by reduction of the nitro group to an amine **6** and reductive removal of the chlorine with 20% Pd/C to give an amino-3-quinoline-carboxylic acid, ethyl ester **7**. The 6-amino isomer of **7** has been previously reported [5]. In the sequence

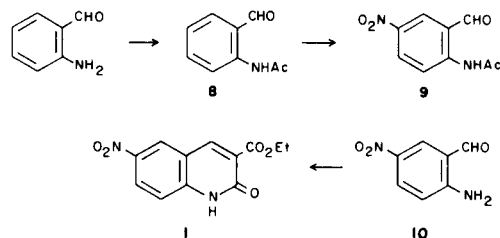
1 → **5** → **6** → **7** the nmr spectral patterns of the benzenoid protons were noted and predictable shifts occurred,

Scheme 2



the regiochemistry was not clear. Immediate clarification was obtained only when the NOE was measured between H4 and H5 of the amino acid ester **7**. Saturating irradiation of the doublet absorption assigned to H4 at δ 8.52 produced a 38% enhancement of the integrated intensity of the *meta* coupled absorption H5 at δ 6.94 without affecting its multiplicity. Because the enhancement effect is inversely proportional to distance, it falls off rapidly and virtually disappears at approximately three angstroms. Since the two hydrogens displaying the enhancement are not spin coupled together, they must be *peri* to one another to remain within the distance constraints. Additionally, because the enhanced absorption represents a *meta* coupled proton, shifted upfield from the normal aromatic position, the main function must be at C6. No other substitution pattern is consistent with these data.

Scheme 3



The second synthetic route (Scheme 3) started with the acetylation of 2-aminobenzaldehyde to give **8**, which was then nitrated according to the procedure of Cohn and

Table 1
¹H NMR Data

Compound	doublet <i>meta</i> H5	doublet of doublets <i>ortho, meta</i> H7	doublet <i>ortho</i> H8	Other Pertinent Peaks
1	8.80	8.35	7.42	8.65 s
2	6.79	6.95	7.11	8.22 s
3	9.00	8.50	7.57	9.05 s
4	6.95	7.12	7.23	8.68 s
5	9.15	8.54	8.13	9.17 s
6	6.99	7.37	7.75	8.51 s
7	6.94	7.30	7.79	8.89 d, 8.52 d
11	8.85	8.35	7.71	8.70 s, 5.14 s
13	8.72	8.33	7.62	8.18 d, 6.78 d, 5.13 s
15	8.80	8.37	7.72	7.98 d, 6.20 d, 5.25 s

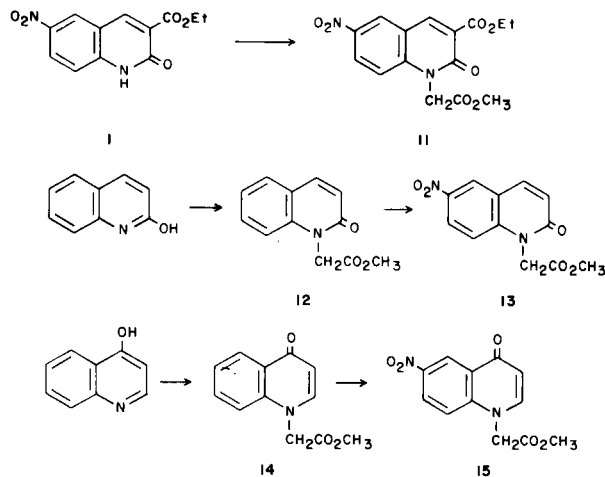
All nmr spectra were run in *d*₆-DMSO solution at 2-4% concentration and the chemical shifts are reported in ppm (δ) relative to the internal standard TMS. The instruments used were a FT Bruker WH-90 or a Varian EM-390 spectrometer. All *meta* coupling constants were 3 Hz and all *ortho* coupling ranged from 9 to 10 Hz.

Springer [6]. The nitration product **9** was acid hydrolyzed to give 2-amino-5-nitrobenzaldehyde **10**. The nmr spectrum of **10** was assigned as follows: H3 at δ 6.82 doublet $J = 10.5$ Hz, H4 at δ 8.07 doublet of doublets $J = 10.5$ and 2.5 Hz, and H6 at δ 8.53 doublet $J = 2.5$ Hz. This pattern is consistent with the 5-nitro-2-aminobenzaldehyde. Further evidence for this structural assignment comes from a comparison of the published spectra [7] for 4- and 5-nitro anthranilic acids. The nearly identical spectral shift values of 5-nitro-2-aminobenzaldehyde and 5-nitroanthranilic acid were definitive. When **10** was condensed with diethylmalonate the product obtained was identical by nmr spectra and elemental analysis to the previously unreported mononitration product **1**; this reaffirms that nitration occurred at C6 as the NOE experiment had determined.

The application of NOE techniques to this isomer question can be simplified by analysis of the spectra of *N*-alkylated derivatives (Scheme 4). For example, compound **1** can be conveniently *N*-alkylated with methyl bromoacetate according to the method of Potts [8], to give compound **11**. Irradiation of the methylene singlet at δ 5.14 provided a 22% NOE enhancement of the *ortho* coupled H8 proton at δ 7.71 and this *ortho* coupling pattern for the H8 proton dictates that the nitro substituent is at C6. To extend the method, both 2-hydroxyquinoline and 4-hydroxyquinoline were *N*-alkylated with methyl bromoacetate and subsequently nitrated to give **13** and **15**. Saturating irradiation of the methylene of **13** at δ 5.13 provided a 23% NOE enhancement of H8 at δ 7.62, the pattern showing only *ortho* coupling. The analogous experiment with **15** involved irradiation of the methylene singlet at δ 5.25, providing a 28% NOE enhancement of the *ortho* coupled H8 proton at δ 7.72. In this experiment an additional 30% NOE enhancement of the H2 proton was observed. These experi-

ments clearly and simply identify the nitration products of the 2- and 4-hydroxyquinolines to be the 6-nitro derivatives.

Scheme 4



EXPERIMENTAL [9]

[(2-Nitrophenyl)methylene]propanedioic Acid, Diethyl Ester.

A solution of 70.8 g (0.47 mole) of *o*-nitrobenzaldehyde, 75.0 g (0.47 mole) of diethylmalonate, 168 ml (1.78 moles) of acetic anhydride, and 70.4 g (0.70 mole) of potassium bicarbonate was heated on a steam bath for two hours. The reaction mixture was poured into 3 ℓ of ice water. After sitting overnight and the solid was collected and dissolved in 1 ℓ of ether. The ether solution was washed with aqueous sodium carbonate and saturated aqueous sodium chloride, dried (magnesium sulfate) and evaporated *in vacuo* to an oil which was recrystallized from 2-propanol to yield 86.8 g (63%) of the title compound, mp 49-51°.

Anal. Calcd. for C₁₄H₁₅NO₆: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.04; H, 5.11; N, 4.85.

1,2-Dihydro-2-oxo-3-quinolinecarboxylic Acid, Ethyl Ester.

A solution of 86.53 g (0.295 mole) of [(2-nitrophenyl)methylene]propionic acid, diethyl ester, and 900 ml of ethanol was hydrogenated over 20 g of Raney nickel [10]. The catalyst was collected by filtration and the filtrate was concentrated to about 300 ml. The solid was collected to give 39.6 g, mp 162-163°. The filtrate was evaporated to dryness and the residue was treated with ether to yield a second crop of 8.9 g, mp 153-156°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.12; H, 5.10; N, 6.32.

1,2-Dihydro-6-nitro-2-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (1).

A solution of 10.0 g (46 mmoles) of 1,2-dihydro-2-oxo-3-quinolinecarboxylic acid, ethyl ester and 50 ml of 96% sulfuric acid was stirred in an ice bath while a cold solution of 9.75 ml of 70% nitric acid and 9.75 ml of 96% sulfuric acid was added dropwise over ten minutes. The reaction solution was stirred with ice bath cooling for one hour and then was poured into ice and water with stirring. The resulting solid was collected by filtration and washed with water and ethanol to yield 10.7 g of **1**, mp >310°.

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 54.50; H, 3.88; N, 10.54.

6-Amino-1,2-dihydro-2-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (2).

A solution of 1.0 g (3.8 mmoles) of **1** in 100 ml of DMF was hydrogenated over 0.5 g of Raney nickel [10]. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* and the residue was triturated with ether and THF to give 0.23 g of **2**, mp 230-231° dec.

Anal. Calcd. for $C_{12}H_{12}N_2O_3 \cdot \frac{1}{3}H_2O$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.44; H, 5.06; N, 11.80.

1,2-Dihydro-6-nitro-2-oxo-3-quinolinecarboxylic Acid (3).

A suspension of 9.7 g (37 mmoles) of **1** in 200 ml of 1*N* sodium hydroxide was heated on the steam bath for 1.25 hours. The suspension was poured over ice and acidified with 250 ml of 1*N* hydrochloric acid. The solid was collected by filtration and washed with water and ethanol to give 8.15 g (94%) of **3**, mp >310°.

Anal. Calcd. for $C_{10}H_6N_2O_5$: C, 51.29; H, 2.58; N, 11.96. Found: C, 51.09; H, 2.68; N, 11.99.

6-Amino-1,2-dihydro-2-oxo-3-quinolinecarboxylic Acid (4).

A solution of 22.5 g (0.0925 mole) of **3** and 400 ml of DMF was hydrogenated over 2 g of Raney nickel [10]. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was triturated with hot methanol and filtered to give 18.3 g of **4**, mp >300°.

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.36; H, 4.10; N, 13.64.

2-Chloro-6-nitro-3-quinolinecarboxylic Acid, Ethyl Ester (5).

A solution of 1.90 g (7.2 mmoles) of **1** and 25 ml of phosphorus oxychloride was heated under reflux for 2.75 hours. The solution was evaporated to dryness and the residue was triturated with ice and water. The solid was filtered and recrystallized from acetonitrile-water to yield 1.14 g of **5**, mp 153-154°.

Anal. Calcd. for $C_{12}H_9ClN_2O_4$: C, 51.35; H, 3.23; N, 9.98. Found: C, 51.13; H, 3.25; N, 9.99.

6-Amino-2-chloro-3-quinolinecarboxylic Acid, Ethyl Ester (6).

A solution of 1.11 g (3.95 mmoles) of **5** in 100 ml of ethanol was hydrogenated over 0.2 g of Raney nickel [10] at 22° and an initial hydrogen pressure of 51.5 psig. The catalyst was collected by filtration, the filtrate was evaporated to dryness and the residue was triturated with isopropyl ether to give 0.57 g of **6**, mp 133-135°.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.17. Found: C, 56.96; H, 4.35; N, 11.07.

6-Amino-3-quinolinecarboxylic Acid, Ethyl Ester (7).

A solution of 0.506 g (2.0 mmoles) of **6**, 0.2 g of potassium acetate, and 75 ml of ethanol was hydrogenated over 0.1 g of 20% Pd/C at 24° and an

initial hydrogen pressure of 50 psig. The catalyst was removed by filtration and the residue was evaporated *in vacuo* to dryness. The residue was recrystallized from ethanol-water to give 0.17 g of **7**, mp 166-168°, lit mp 167-168° [5].

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.44; H, 5.56; N, 13.05.

N-(2-Formylphenyl)acetamide (8).

A solution of 8.1 g (54 mmoles) of 2-aminobenzaldehyde, 9 ml (95 mmoles) of acetic anhydride and 10 ml of ether was stirred at room temperature for 23 hours. The reaction mixture was evaporated *in vacuo* to dryness and the residue was recrystallized from water to give 3.6 g, mp 68-69° of **8** and an additional 3.0 g, mp 69-71° was obtained by concentrating the filtrate.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 65.95; H, 5.26; N, 8.42.

N-(2-Formyl-4-nitrophenyl)acetamide (9).

A solution of 1.1 g (6.7 mmoles) of **8**, 1.0 ml of acetic acid and 5.5 ml of sulfuric acid was cooled with an ice bath and a mixture of 1.5 ml of 70% nitric acid and 1.5 ml 96% sulfuric acid was added dropwise. The solution was stirred in the cold for 0.5 hour and then at room temperature for four hours. It was poured into ice and water and the solid was collected by filtration to give 1.5 g of **9**, mp 151-154°. An analytical sample was recrystallized from ethanol, mp 158-159°.

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.00; H, 3.72; N, 13.27.

2-Amino-5-nitrobenzaldehyde (10).

A solution of 1.5 g (7.2 mmoles) of **9** and 10 ml of hydrochloric acid was heated on a steam bath for 1.5 hours. The mixture was poured into ice and water and the solid was collected by filtration to give 0.92 g of **10**, mp ~300° dec.

Anal. Calcd. for $C_7H_6N_2O_3$: C, 50.61; H, 3.64; N, 16.86. Found: C, 50.49; H, 3.75; N, 16.85.

1,2-Dihydro-6-nitro-2-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (1).

A solution of 0.88 g (5.3 mmoles) of **10** and 5 g (31 mmoles) of diethylmalonate was heated at 150-160° in an oil bath for 17.5 hours. The reaction mixture was cooled to room temperature and filtered to give 0.18 g of **1**.

Anal. Calcd. for $C_{12}H_{10}N_2O_5 \cdot 0.5H_2O$: C, 53.14; H, 4.09; N, 10.33. Found: C, 53.51; H, 3.65; N, 10.43.

3-Ethoxycarbonyl-6-nitro-2-oxo-1(2*H*)-quinolineacetic Acid, Methyl Ester (11).

A solution of 1.31 g (5.0 mmoles) of **1**, 2.1 ml (25 mmoles) of methyl bromoacetate, 1.04 g (7.5 mmoles) of potassium carbonate, and 50 ml of dimethylformamide was stirred at room temperature for 18 hours. The reaction mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was treated with hot ethanol and filtered to give 0.30 g of mp 204-206°, and an additional 0.80 g of **11** crystallized from the filtrate.

Anal. Calcd. for $C_{15}H_{14}N_2O_7$: C, 53.90; H, 4.22; N, 8.38. Found: C, 53.68; H, 4.19; N, 8.29.

2-Oxo-1(2*H*)-quinolineacetic Acid, Methyl Ester (12).

To a suspension of 1.1 g (23 mmoles) of 50% sodium hydride and 30 ml of benzene was added a suspension of 1.45 g (10 mmoles) of 2-hydroxyquinoline in 30 ml of benzene. The mixture was stirred at room temperature for ten minutes and 0.84 g (10 mmoles) of methyl bromoacetate was added. The mixture was heated under reflux for two hours and then poured over 20 ml of 1*N* hydrochloric acid and ice. The benzene layer was separated, dried (magnesium sulfate) evaporated *in vacuo* to dryness, and the residue was triturated with ether to give 0.80 g of **12**, mp 121-123°. The ether filtrate was concentrated *in vacuo* and the residue was recrystallized from ethyl acetate-hexane to give 0.45 g of **12**, mp 123-125°.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.14; H, 5.12; N, 6.25.

6-Nitro-2-oxo-1(2*H*)-quinolineacetic Acid, Methyl Ester (**13**).

To a cold solution of 0.67 g (3.1 mmoles) of **12** in 5 ml of sulfuric acid was added dropwise a nitrating mixture of 1 ml of 96% sulfuric acid and 1 ml 70% nitric acid. The solution was stirred at 0° for 1.75 hours and poured into 100 ml of ice and water. The crude product was collected by filtration and recrystallization from methanol yielded 0.35 g of **13**, mp 210-212° dec.

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 54.74; H, 3.95; N, 10.45.

4-Oxo-1(4*H*)-quinolineacetic Acid, Methyl Ester (**14**).

A solution of 3.65 g (18.3 mmoles) of 4-hydroxyquinoline trihydrate, 14.0 g (91.6 mmoles) methyl bromoacetate, 3.8 g (27.5 mmoles) potassium carbonate and 75 ml of *N,N*-dimethylformamide was stirred at room temperature for 21 hours. The reaction mixture was filtered and the filtrate was concentrated to an oil which was recrystallized from ethyl acetate to give 1.28 g of (**14**), mp 155-156°. An additional 1.56 g of **14**, mp 153-155° was obtained from the filtrate.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.30; H, 5.07; N, 6.28.

6-Nitro-4-oxo-1(4*H*)-quinolineacetic Acid, Methyl Ester (**15**).

To a cold solution of 1.00 g (4.6 mmoles) of **14** in 10 ml of 96% sulfuric acid was added dropwise a nitrating mixture of 1.5 ml sulfuric acid and 1.5 ml 70% nitric acid. The solution was stirred at 0° for 1.5 hours and then poured into 100 ml of ice and water. The solid was collected by filtration and washed with water and ethanol to give 0.89 g **15**, mp 219-221°.

Anal. Calcd. for $C_{12}H_{10}N_2O_5 \cdot \frac{1}{4}H_2O$: C, 54.04; H, 3.97; N, 10.50. Found: C, 54.11; H, 3.90; N, 10.85.

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- [7] Sadtler Standard Spectra: #14647 4-nitroanthranilic acid: H-3 7.67 δ *meta* coupling, H-5 7.16 δ *ortho* and *meta* coupling, H-6 7.96 δ *ortho* coupling; #10976 5-nitroanthranilic acid: H-3 6.91 δ *ortho* coupling, H-4 8.10 δ *ortho* and *meta* coupling, H-6 8.66 δ *meta* coupling; [b] Compound **10**, 2-amino-5-nitrobenzaldehyde: H-3 6.90 δ *ortho* coupled, H-4 8.15 δ *ortho* and *meta* coupled, H-6 8.60 δ *meta* coupled.
- [8] K. T. Potts and S. Yao, *J. Org. Chem.*, **44**, 977 (1979).
- [9] All melting points are uncorrected and were taken in an open capillary tube with a Thomas Hoover melting point apparatus.
- [10] Number 30 Raney Nickel catalyst from W. R. Grace Company was used.