The combined extracts were dried ($MgSO_4$), and the solvent was removed on a rotary evaporator, leaving 22 g of a dark oil. The oil was treated with formaldehyde and pyrrolidine in the same manner as compound 1. Silica gel column chromatography, eluting with EtOAc/MeOH/NH_4OH (50:1:0.05), afforded an oil that crystallized on standing. Recrystallization from EtOAc yielded 2.8 g (6.0%) of pale yellow crystals: mp 162–163 °C; NMR (CD_3OD) δ 1.5–2.0 (m, 8 H), 2.3–2.7 (m, 8 H), 3.63 (s, 4 H), 6.77 (s, 2 H), 7.3–7.8 (m, 5 H).

2,6-Bis(1-pyrrolidinylmethyl)-4-benzamidophenol (7). By use of the procedure of Chipalkatti et al.,[11] a mixture of 10.0 g (72.5 mmol) of *p*-hydroxybenzoic acid, 10 mL (110 mmol) of aniline, and 5.0 g (35 mmol) of P_2O_5 in 100 mL of toluene was heated to reflux under a nitrogen atmosphere for 3 h. The solvent was removed on a rotary evaporator, leaving a white solid. Purification by silica gel column chromatography using a Waters Prep 500 and eluting with ethyl acetate afforded a yellow solid. Crystallization from ethyl acetate/ethanol gave 3.5 g (23%) of white crystals: mp 198–200 °C. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.52; H, 5.36; N, 6.55.

The product was treated with formaldehyde and pyrrolidine in the same manner as compound 1. Purification by MPLC and crystallization from ethanol resulted in an overall 11% yield of white crystals of free base: mp 154–155 °C; NMR ($CDCl_3$) δ 1.6–2.1 (m, 8 H), 2.4–2.9 (m, 8 H), 3.77 (s, 4 H), 6.9–8.1 (m, 8 H), 9.67 (6 s, 1 H).

Compound 8 (yield, 4.5%; crystallization solvent, EtOH), 9 (2.0%, EtOH), and 10 (14%; EtOH) were prepared similarly.

2,6-Bis(1-pyrrolidinylmethyl)-4-(*N*-methylbenzamido)phenol (11). A mixture of 10 g (73 mmol) of *N*-methyl-*p*-anisidine in 90 mL of 48% HBr was heated to reflux for 6 h. The mixture was evaporated to dryness on a rotary evaporator, leaving *p*-hydroxy-*N*-methylaniline as an off-white solid. Neutralization with NH_4OH gave the free base as a dark solid: NMR (CD_3OD) δ 2.5 (s, 3 H), 6.1–6.6 (m, 4 H).

A solution of 4.5 g (36 mmol) of product, 5.5 g (36 mmol) of *tert*-butyldimethylsilyl chloride and 9.8 g (140 mmol) of imidazole in 20 mL of dimethylformamide was heated to 55 °C for 5 h. Water was added and the mixture was extracted with dichloromethane. Th combined extracts were washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The CH_2Cl_2 was removed on a rotary evaporator and the remaining DMF was removed with a vacuum pump, leaving 7.0 g of 18 as a dark oil: NMR ($CDCl_3$) δ 0.24 (s, 6 H), 1.03 (s, 9 H), 2.81 (s, 3 H), 3.46 (br s, 1 H), 6.4–6.8 (m, 4 H).

The protected hydroxyaniline 18 (7.0 g, 2.9 mmol) was dissolved in 50 mL of dioxane and 20 mL (140 mol) of triethylamine was added. The solution was cooled to 0 °C and 4.1 g (29 mol) of benzoyl chloride in 30 mL of dioxane was added dropwise. The mixture was allowed to warm to ambient temperature. After 18 h the mixture was filtered and the solvent was removed on a rotary evaporator, leaving 10.2 g of 19 as a dark oil: IR (film) 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.22 (s, 6 H), 1.05 (s, 9 H), 3.42 (s, 3 H), 6.6–7.6 (m, 9 H).

The protected hydroxybenzamide 19 (9.9 g, 29 mmol) was cooled to 0 °C and then treated with 58 mL (58 mmol) of a 1 M solution of tetra-*n*-butylammonium fluoride in THF. The solution was stirred and allowed to warm to ambient temperature over 1 h. Water was added and the organic layer was separated. The solvent was removed on a rotary evaporator, leaving 4.5 g of the phenol product as a dark oil. An NMR spectrum confirmed that the protecting group had been removed.

The product was treated with formaldehyde and pyrrolidine in the same manner as compound 1. Purification of the product by silica gel column chromatography, eluting with EtOAc/MeOH/NH_4OH (9:1:0.05), afforded 3.9 g of product as a dark brown oil. The oil was taken up in ether and the solution was saturated with hydrogen chloride, which caused white crystals to precipitate. The crystals were collected and dried, giving 3.0 g of a very hygroscopic product 11: mp 63–65 °C; NMR (D_2O) δ 1.6–2.3 (m, 8 H), 2.6–3.7 (m) and 3.47 (s, total 11 H), 4.37 (s, 4 H), 7.23 (s), and 7.33 (s, total, 7 H).

Compounds 16 (yield, 12%; crystallization solvent, CH_2Cl_2/Et_2O) and 17 (41%, EtOAc (free base)) were prepared by treating *N*-(*p*-hydroxyphenyl)benzamide[3] with piperidine or morpholine, respectively, and formaldehyde in the same manner as compound 1.

Registry No. 1, 94042-51-0; 1 (free base), 94042-65-6; **2**, 90446-35-8; **2** (free base), 90446-34-7; **3**, 94042-52-1; 4, 94042-53-2; **5**, 94042-54-3; **6**, 94042-55-4; **7**, 90446-66-5; **8**, 94042-56-5; **9**, 94042-57-6; **10**, 94042-58-7; 11, 90446-73-4; 11 (free base), 90446-70-1; **12**, 90446-37-0; **12** (free base), 90446-36-9; **13**, 94042-59-8; **13** (free base), 94042-63-4; 14, 94042-60-1; 14 (free base), 94042-64-5; **15**, 94042-61-2; **16**, 90446-65-4; **16** (free base), 81079-98-3; **17**, 90446-64-3; **17** (free base), 81080-00-4; **18**, 90446-71-2; **19**, 90446-72-3; *p*-(benzyloxy)phenol, 103-16-2; *p*-hydroxydiphenylamine, 122-37-2; *p*-hydroxybenzophenone, 1137-42-4; 4-hydroxy-4′-methoxybenzophenone, 61002-54-8; 4-chloro-4′-hydroxybenzophenone, 42019-78-3; 4,4′-dihydroxybenzophenone, 611-99-4; o-toluidine, 95-53-4; 2,6-dimethylaniline, 87-62-7; 2-aminothiazole, 96-50-4; *p*-hydroxybenzoic acid, 99-96-7; *p*-hydroxy-*N*-(2-methylphenyl)benzamide, 62639-21-8; *p*-hydroxy-*N*-(2,6-dimethylphenyl)benzamide, 51616-07-0; *p*-hydroxy-*N*-(2-thiazoyl)benzamide, 94042-62-3; 4-hydroxydiphenylmethane, 101-53-1; pyrrolidine, 123-75-1; *p*-aminophenol, 123-30-8; phenyl isocyanate, 103-71-9; (4-hydroxyphenyl)-phenylurea, 2298-29-5; cinnamoyl chloride, 102-92-1; *p*-hydroxy-*N*-cinnamylbenzamide, 3579-85-9; benzenesulfonyl chloride, 98-09-9; *N*-(*p*-hydroxyphenyl)benzenesulfonamide, 5471-90-9; aniline, 62-53-3; *p*-hydroxy-*N*-phenylbenzamide, 14121-97-2; *N*-methyl-*p*-anisidine, 5961-59-1; *p*-hydroxy-*N*-methylaniline, 150-75-4; benzoyl chloride, 98-88-4; *N*-methyl-*N*-(*p*-hydroxyphenyl)benzamide, 70489-16-6; *N*-(*p*-hydroxyphenyl)benzamide, 15457-50-8; piperidine, 110-89-4; morpholine, 110-91-8.

(11) Chipalkatti, V. B.; Manivannan, K.; Desai, R. M.; Gopal, M. *Ind. 69, 680* (*Chem. Abstr.* **1962**, 57P, 15031e).

Synthesis and Antiallergic Activity of Some Quinolinones and Imidazoquinolinones

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A group of 1,4-dihydro-4-oxoquinoline-2- and -3-carboxylic acid esters with nitrogen functionality at the 8-position was synthesized, and 6-oxo-6*H*-imidazo[4,5,1-*ij*]quinoline-4- and -5-carboxylic acid esters were elaborated from these. Several of the compounds displayed activity in the rat passive cutaneous anaphylaxis (PCA) test for antiallergic activity. However, PCA activity in this series was accompanied by rat toxicity, as measured by a decrease in percent of normal weight gain over a 2-week period, following a single oral dose.

Clinical experience with disodium cromoglycate (DSCG) for nearly 20 years has demonstrated that this compound is an effective, prophylactic agent for the treatment of asthma.[1] Although DSCG is a mediator release inhibitor,[1]

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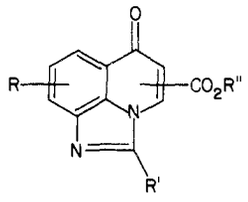
recent reports suggest additional modes of action for this drug.[2] Since DSCG is active by inhalation only, considerable effort has centered on finding an orally active replacement.[3]

One generalized structure for mediator release inhibitors has been proposed by Cheney et al.[4,5] Although this structure does not accommodate all of the known mediator release inhibitors, it is a helpful guide in summarizing salient structural features of a large subset of mediator release inhibitors. Included in this subset are the chromones (i.e., DSCG) and 1,4-dihydro-4-oxoquinoline-2- and -3-carboxylic acids.[6] We have recently prepared peri-fused tricyclic systems related to the oxoquinolinecarboxylic acids. We now report the preparation and antiallergic activity of 6-oxo-6*H*-imidazo[4,5,1-*ij*]quinoline-5- and -6-carboxylic acid derivatives (general structure 1) and related compounds.



1

Chemistry. The synthesis of 6-oxo-6*H*-imidazo[4,5,1-*ij*]quinoline-4-carboxylic acid methyl ester was accomplished as shown in Scheme I.[7] Treatment of 2-nitroaniline (**2**) with dimethyl acetylenedicarboxylate (**3**) gave enamine 4, which was cyclized to 1,4-dihydro-8-nitro-4-oxo-2-quinolinecarboxylic acid methyl ester (**5**) with either phosphoric acid (PPA) or thermally in Dowtherm A. Catalytic reduction of **5** gave the corresponding amino compound **7**, after drying.[8] On treatment with triethyl

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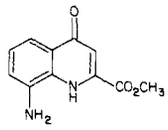
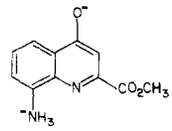
(2) Johnson, P. C.; Gillespie, E.; Temple, D. L. In "Annual Reports in Medicinal Chemistry"; Hess, H. J., Comer, W. T., Eds.; Academic Press: New York, 1982; Vol. 17, p 55.
(3) Wasley, J. W. F. In "Medicinal Chemistry Advances"; De Las Heras, F. G.; Vega, S., Eds.; Pergamon Press: Oxford, England, 1981; pp 329–343.
(4) Cheney, B. V.; Wright, J. B.; Hall, C. M.; Johnson, H. G. *J. Med. Chem.* **1978**, *21*, 936.
(5) Cheney, B. V.; Duchamp, D. J.; Christoffersen, R. E. *J. Med. Chem.* **1983**, *26*, 719.
(6) Hall, C. M.; Johnson, H. G.; Wright, J. B. *J. Med. Chem.* **1974**, *17*, 685.
(7) The general method used for the synthesis of **7** in Scheme I has previously been described by Heindel et al.: Heindel, N. D.; Bodof, T. A.; Kogelschatz, J. E. *J. Heterocycl. Chem.* **1966**, *3*, 222.
(8) Infrared spectral data indicated that monohydrate **6** exists in the dihydroquinolone form and that **7** exists in the hydroxyquinoline zwitterionic form. The infrared spectrum of **6** showed NH and OH (water) stretching at 3600–3100 cm^{-1}, ester carbonyl stretching at 1740 cm^{-1}, and ketone stretching at 1680 cm^{-1}. Removal of water led to a significant change. Compound **7** displayed NH (protonated amine) stretching at 3500–2000 cm^{-1}. Ester carbonyl stretching appeared at 1735 cm^{-1}, and ketone stretching was *absent*. We have drawn quinolone rather than hydroxyquinoline structures in the schemes for consistency.

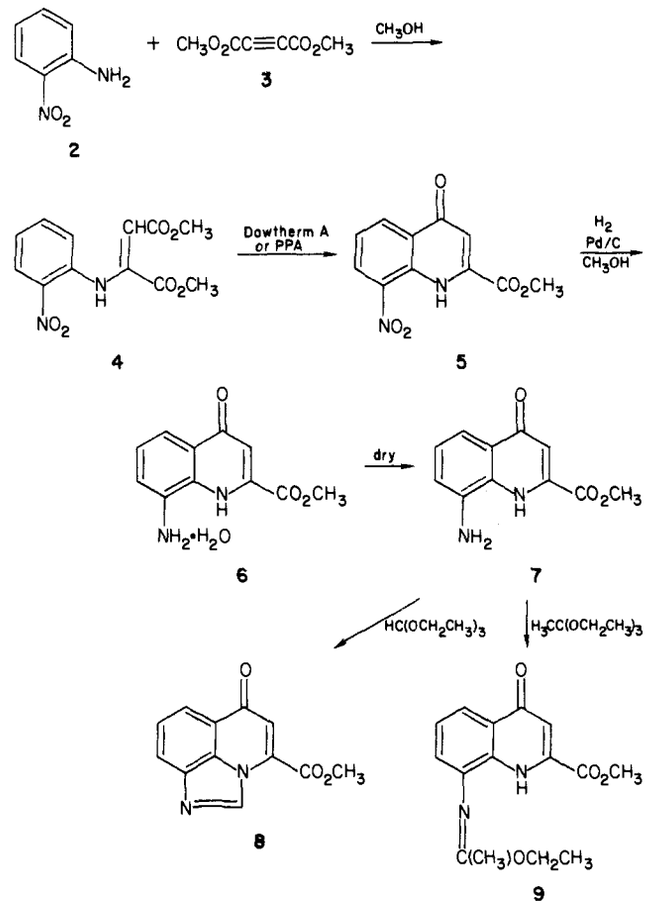


dihydroquinolone form



hydroxyquinoline zwitterionic form

Scheme I



Scheme II

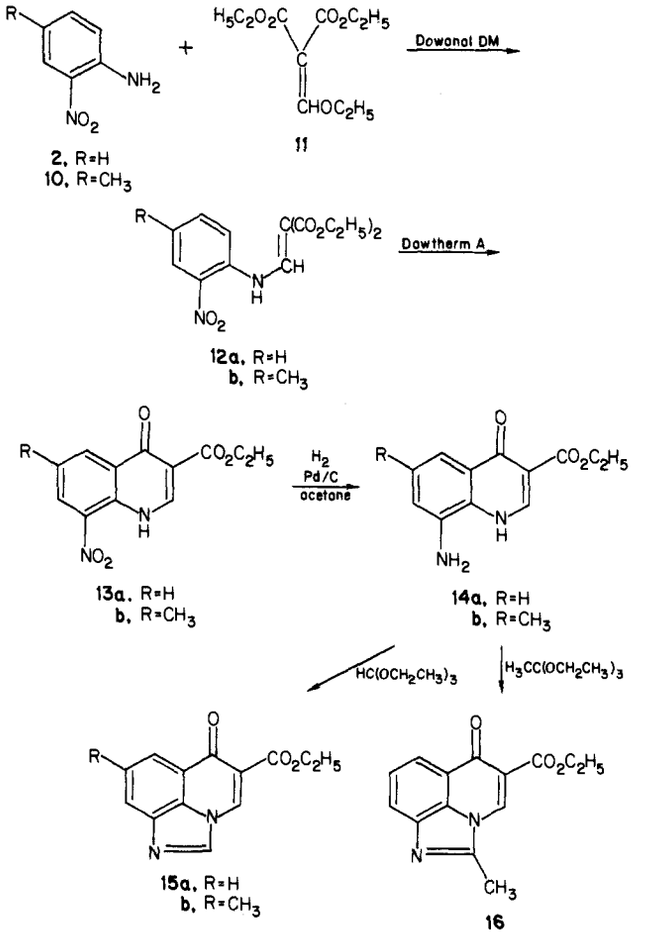
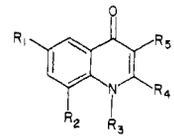


Table I. Biological Activity of Quinolinone and Imidazoquinolinone Derivatives



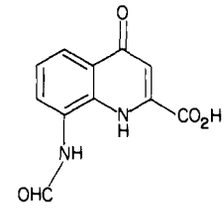
no.	R_1	R_2	R_3	R_4	R_5	rat PCA test ip[a]	rat PCA test po[b]	% normal wt gain[c]
5	H	O_2N	H	CO_2CH_3	H	66 ± 14 ($p < 0.01$)	8 ± 5	104 ± 8
6	H	H_2N	H	CO_2CH_3	H	10 ± 12	3 ± 4	100 ± 7
8	H	N=CH		CO_2CH_3	H	16 ± 8	1 ± 7	68 ± 4 ($p < 0.01$)
9	H	EtO(Me)C=N	H	CO_2CH_3	H	24 ± 6 ($p < 0.01$)		
17	H	OHCNH	H	COOH	H	91 ± 5 ($p < 0.01$)	16 ± 4 ($p < 0.01$)	
13a	H	O_2N	H	H	$CO_2C_2H_5$	13 ± 5	−2 ± 9	106 ± 7
14a	H	H_2N	H	H	$CO_2C_2H_5$	19 ± 8		86 ± 12
14b	CH_3	H_2N	H	H	$CO_2C_2H_5$	−2 ± 2		
15a	H	N=CH		H	$CO_2C_2H_5$	100 ± 0 ($p < 0.01$)	70 ± 7 ($p < 0.01$)	−6 ± 11 ($p < 0.005$)
15b	CH_3	N=CH		H	$CO_2C_2H_5$	3 ± 13	70 ± 13 ($p < 0.01$)	
16	H	$N=CCH_3$		H	$CO_2C_2H_5$	95 ± 5 ($p < 0.01$)	83 ± 10 ($p < 0.01$)	−49 ± 18 ($p < 0.005$)
18	H	OHCNH	H	H	COOH	62 ± 7 ($p < 0.01$)	0 ± 16	
19	H	OHCNH	H	H	$CO_2C_2H_5$	67 ± 15 ($p < 0.01$)	76 ± 16 ($p < 0.01$)	−26 ± 12 ($p < 0.005$)
DSCG						100 ± 0 ($p < 0.01$)	2 ± 5	

[a] Animals dosed at 60 mg/kg. [b] Animals dosed at 100 mg/kg. [c] Animals were dosed with 200 mg/kg (po) of the test compound on day one of the 2-week study.

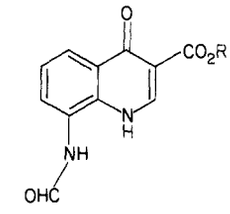
orthoformate, **7** gave 6-oxo-6*H*-imidazo[4,5,1-*ij*]-quinoline-4-carboxylic acid methyl ester (**8**) in good yield. However, treatment of **7** with triethyl orthoacetate afforded a good yield of imino ether **9** rather than the desired 2-methyl derivative of **8**. This result is similar to our earlier experiences[9,10] wherein we were able to produce fused triazepine systems from acyclic precursors and triethyl orthoformate but unable to produce the homologous systems with triethyl orthoacetate. Attempted cyclization of **9**, using *p*-toluenesulfonic acid as a catalyst, led only to the recovery of unchanged **9**.

Scheme II[11] outlines the preparation of 6-oxo-6*H*-imidazo[4,5,1-*ij*]quinoline-5-carboxylic acid ethyl ester (**15a**), as well as its 2-methyl (**16**) and 8-methyl (**15b**) derivatives. Ene diesters **12a** and **12b** were prepared by treating 2-nitroaniline (**2**) and 4-methyl-2-nitroaniline (**10**), respectively, with diethyl ethoxymethylenemalonate (**11**) in Dowanol DM. Thermal cyclization of **12a** and **12b** in Dowtherm A afforded the respective nitroquinolines **13a** and **13b**, which afforded aminoquinolines **14a** and **14b**, respectively, after catalytic hydrogenation. Imidazoquinolines **15a** and **15b** were then produced from **14a** and **14b**, respectively, by treatment with triethyl orthoformate. Likewise, treatment of **14a** with triethyl orthoacetate readily produced imidazoquinoline **16**. This result is interesting in view of the lack of imidazoquinoline formation from **7** and triethyl orthoacetate. Perhaps the quinoline nitrogen of **7** is less nucleophilic or reactive than that of **14a** because of steric or electronic factors, or both.

The results of hydrolytic experiments on imidazoquinoline esters **8** and **15a** are summarized by structures **17–19**. Treatment of **8** with sodium hydroxide gave carboxylic acid **17** in which the imidazo ring had opened to produce a formylamino unit. Similarly, **15a** and sodium hydroxide produced formylamino acid **18**. It was also determined that imidazo ring opening would occur with acid. Treatment of **15a** with *p*-toluenesulfonic acid in acetic acid gave formylamino ester **19**.



17



18, R=H
19, R=CH_3

Results and Discussion

The compounds described were evaluated for antiallergic activity in the rat passive cutaneous anaphylaxis (PCA) test, and the results are reported in Table I. When compounds had significant activity following ip administration (60 mg/kg), or were of interest for struvture–activity reasons, they were also tested for oral activity at a dose of 100 mg/kg. With the exception of compound **5**, it seemed apparent that a substituted-amino group was required at the 8-position for compounds to produce inhibition when administered by the intraperitoneal route. Biologically significant antiallergic activity following oral administration of compounds was only seen when both a substituted amine and an ester function were present on positions 8 and 3, respectively. When an acid instead of an ester was located on position 3 (**18** compared to **19**), no

(9) Peet, N. P.; Sunder, S. *J. Heterocycl. Chem.* **1976**, *13*, 967.
(10) Peet, N. P.; Sunder, S. *J. Heterocycl. Chem.* **1977**, *14*, 1147.
(11) The general method employed for the synthesis of **13a** and **13b** in Scheme II has previously been described by Price, C. C.; Roberts, R. M. *J. Am. Chem. Soc.* **1946**, *68*, 1204.
(12) Goose, J.; Blair, A. M. J. N. *Immunology* **1969**, *16*, 749.

demonstrable oral activity was present even though both compounds had comparable ip activity, suggesting that the free acid was not absorbed following oral administration.

Imidazoquinoline **15a**, the most active compound in the series, was selected to undergo further development. Subsequently, it was found to reduce the normal rate of weight gain as well as cause severe nephrotoxicity. Several compounds in the series, including both active and inactive compounds, were then examined for their effects on the rate of weight gain of rats following a single oral dose of 200 mg/kg. Compounds which altered weight gain produced a statistically significant effect within 4 days after compound administration. Consequently, percent of normal weight gain for the first 4 days after compound administration is presented in Table I as an indication of the toxicity of the compound. It is apparent from the data that a significant reduction in weight gain was seen only in those compounds that have a substituted amine at the 8-position. Since this substitution was also a requirement for oral activity in the rat PCA test, it does not seem likely that desirable pharmacological activity can be separated from toxicity in this series of quinolinones and imidazoquinolinones.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The structure of all compounds was confirmed by IR, ^{1}H NMR, and mass spectroscopy and combustion analysis. IR spectra were recorded with a Perkin-Elmer Model 727B spectrophotometer, ^{1}H NMR spectra with Varian EM-360A and Perkin-Elmer R-32 (90 MHz) spectrometers, and mass spectra with a Finnigan GC/MS Model 4023 [electron impact (EI) and methane chemical ionization (CI)] mass spectrometer at 70 eV. Combustion analyses for C, H, and N were performed by Dow Analytical laboratories, Midland, MI. Dowtherm A is a eutectic mixture of biphenyl (26.5%) and diphenyl ether (73.5%). Dowanol DM is 2-(2-methoxyethoxy)-ethanol.

2-[(2-Nitrophenyl)amino]-2-butenedioic Acid Dimethyl Ester (4). To a solution of **2** (13.8 g, 0.100 mol) in 150 mL of MeOH was added **3** (15.6 g, 0.110 mol). After 18 h of stirring, the mixture was heated at reflux for 6 h and cooled, and the resulting yellow prisms were collected to yield 21.3 g (76%) of **4**: mp 131–132.5 °C; IR (Nujol) 3260 (NH), 1730 (C=O), 1670 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3, CH_3), 3.76 (s, 3, CH_3), 5.76 (s, 1, vinyl), 7.55–6.58 (m, 3, aromatic), 8.09–7.88 (m, 1, aromatic), 11.08 (br s, 1, NH). Anal. ($C_{12}H_{12}N_2O_6$) C, H, N.

1,4-Dihydro-8-nitro-4-oxo-2-quinolinecarboxylic Acid Methyl Ester (5). Dowtherm A Method. Ene diester **4** (17.4 g, 62.1 mmol) was added in portions to 200 mL of Dowtherm A at 240 °C. After 5 min at 240–250 °C, the solution was cooled to 10 °C, diluted with an equal volume of ether, and refrigerated overnight. The resulting brown needles were collected to give 5.54 g (36%) of **5**: mp 194–196 °C (Me_2SO–H_2O); IR (Nujol) 3340 (NH), 1735 (C=O), 1640 (C=O) cm^{-1}; ^{1}H NMR (CF_3CO_2H) δ 4.30 (s, 3, CH_3), 8.31–7.90 (m, 2, aromatic), 9.30–8.90 (m, 2, aromatic). Anal. ($C_{11}H_8N_2O_5$) C, H, N.

Polyphosphoric Acid Method. A mixture of **4** (50.0 g, 0.178 mol) and 300 g of PPA was heated at 120 °C for 1 h. The solution was cooled and poured into Na_2CO_3 solution and the resulting yellow solid was collected to give 29.2 g (66%) of **5**: mp 198–199 °C (Me_2SO–H_2O).

8-Amino-1,4-dihydro-4-oxo-2-quinolinecarboxylic Acid Methyl Ester (7). A slurry of **5** (6.48 g, 56.1 mmol) and 350 mg of 5% Pd/C in 200 mL of MeOH was hydrogenated in a Parr apparatus at ca. 50 psi for 30 min. The catalyst was removed by filtration and the filtrate was concentrated to leave 5.62 g (91%) of **6**: mp 132–140 °C (melt and resolidify), 175–178 °C (EtOH–H_2O); IR (Nujol) 3600–3100, 1740 (C=O), 1680 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.90 (s, 3, CH_3), 7.09–6.75 (m, 1, aromatic), 7.44–7.09 (m, 3, aromatic). Anal. ($C_{11}H_{10}N_2O_3 \cdot H_2O$) C, H, N. Monohydrate **6** (brown prisms) was oven-dried to give **7** (tan crystals): mp 175–178 °C; IR (Nujol) 3500–2000 (NH_3^+), 1735 (C=O) cm^{-1}. Anal. ($C_{11}H_{10}N_2O_3$) C, H, N.

6-Oxo-6*H*-imidazo[4,5,1-*ij*]quinoline-4-carboxylic Acid Methyl Ester (8). Amino ester **7** (2.50 g, 11.5 mmol) and 25 mL of triethyl orthoformate were heated at reflux for 12 h. The mixture was cooled and the solid was collected to give 2.30 g (88%) of **8**: mp 198–200 °C (EtOH); IR (Nujol) 1730 (C=O), 1645 (C=O), 1635 (C=N) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 4.08 (s, 3, CH_3), 6.89 (s, 1, C5 H), 7.66 (t, J = 8 Hz, 1, C9 H), 7.99 (d, J = 8 Hz, 1, C10 H), 8.14 (d, J = 8 Hz, 1, C7 H), 9.05 (s, 1, C2 H); MS (CI) 229 (M^+ + 1), 257 (M^+ + 29), 269 (M^+ + 41). Anal. ($C_{12}H_8N_2O_3$) C, H, N.

8-[(1-Ethoxyethylidene)amino]-1,4-dihydro-4-oxo-2-quinolinecarboxylic Acid Methyl Ester (9). A mixture of **7** (0.500 g, 2.29 mmol) and 25 mL of triethyl orthoacetate was heated at reflux for 17 h. The mixture was cooled and the solid collected to give 0.540 g (82%) of **9**: mp 166–167 °C (EtOH); ^{1}H NMR (Me_2SO-d_6) δ 1.38 (t, J = 7 Hz, 3, CH_2CH_3), 1.98 (s, 3, N=CCH_3), 3.96 (s, 3, OCH_3), 4.37 (q, J = 7 Hz, 2, CH_2), 6.63 (s, 1, C3 H), 7.46–7.13 (m, 3, aromatic), 7.94–7.74 (m, 1, C5 H), 9.55 (s, 1, NH); MS (CI) 289 (M^+ + 1), 317 (M^+ + 29), 329 (M^+ + 41). Anal. ($C_{15}H_{16}N_2O_4$) C, H, N.

[[(2-Nitrophenyl)amino]methylene]propanedioic Acid Diethyl Ester (12a). A solution of 2-nitroaniline (69.1 g, 0.500 mol) and diethyl ethoxymethylenemalonate (151 g, 0.700 mol) in 25 mL of Dowanol DM was heated at reflux for 2.5 h. The solution was cooled and diluted with EtOH until crystallization commenced. The yellow solid was collected and recrystallized (EtOH–H_2O) to give 66.4 g (43%) of **12a**: mp 100–101 °C (lit.[13] mp 101–102 °C); IR (Nujol) 3190 (NH), 1690 (C=O), 1650 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.52–1.22 (m, 6, CH_3 groups), 4.56–4.15 (m, 4, CH_2 groups), 7.35–7.10 (m, 1, C4 H), 7.85–7.41 (m, 2, C5 H and C6 H), 8.38–8.19 (m, 1, C3 H), 8.52 (d, J = 13 Hz, 1, NHC*H*); MS (CI) 309 (M^+ + 1), 337 (M^+ + 29). Anal. ($C_{14}H_{16}N_2O_6$) C, H, N.

The 4-methyl analogue of **12a** (**12b**) was prepared from **10** (83% yield) in similar fashion: mp 129–131 °C (EtOH). Anal. ($C_{15}H_{18}N_2O_6$) C, H, N.

1,4-Dihydro-8-nitro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (13a). A solution of **20a** (30.8 g, 0.100 mol) in 300 mL of Dowtherm A was heated at 240 °C for 5 h. The solution was cooled and the resulting yellow solid was collected and washed with Et_2O to give 20.0 g (76%) of **13a**: mp 251–253 °C (EtOH) (lit.[13] mp 252–253 °C); IR (Nujol) 3200 (NH), 1710 (C=O) cm^{-1}.

The 6-methyl analogue of **13a** (**13b**) was prepared from **12b** (64% yield) in similar fashion: mp 239–240 °C. Anal. ($C_{13}H_{12}N_2O_5$) C, H, N.

8-Amino-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (14a). A solution of **13a** (4.00 g, 15.3 mmol) in 200 mL of warm HOAc containing 500 mg of 10% Pd/C was hydrogenated on a Parr apparatus at ca. 50 psi until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate was concentrated to a small volume. The resulting solid was collected to give 2.85 g (80%) of **14a**: mp 229–231 °C (EtOH); IR (Nujol) 3450, 3370, 3260, 1700 (C=O) cm^{-1}. Anal. ($C_{12}H_{12}N_2O_3$) C, H, N.

The 6-methyl analogue of **14a** (**14b**) was prepared from **13b** (70% yield) in similar fashion: mp 239–240 °C.

6-Oxo-6*H*-imidazo[4,5,1-*ij*]quinoline-5-carboxylic Acid Ethyl Ester (15). A solution of **14a** (2.00 g, 8.61 mmol) in excess triethyl orthoformate was heated at reflux for 15 h. The solution was cooled and the resulting precipitate was collected to give 1.60 g (77%) of **15a**: mp 198 °C (EtOH); IR (Nujol) 1680 (C=O), 1650 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.35 (t, J = 7.5 Hz, 3, CH_3), 4.37 (q, J = 7.5 Hz, 2, CH_2), 7.90 (t, J = 8 Hz, 1, C8 H), 8.22–8.03 (m, 1, C9 H), 8.43–8.22 (m, 1, C7 H), 9.03 (s, 1, C4 H), 9.39 (s, 1, C2 H). Anal. ($C_{13}H_{10}N_2O_3$) C, H, N.

The 8-methyl analogue of **15a** (**15b**) was prepared from **14b** (94% yield) in similar fashion: mp 241–242 °C (EtOH). Anal. ($C_{14}H_{12}N_2O_3$) C, H, N.

2-Methyl-6-oxo-6*H*-imidazo[4,5,1-*ij*]quinoline-5-carboxylic Acid Ethyl Ester (16). A mixture of **14a** (2.30 g, 9.90 mmol)

(13) Riegel, B.; Lappin, G. R.; Adelson, B. H.; Jackson, R. I.; Albisetti, C. J.; Dodson, R. M.; Baker, R. H. *J. Am. Chem. Soc.* **1946**, *68*, 1264.

and 20 mL of triethyl orthoacetate was heated at reflux for 15 h. The new mixture which resulted was concentrated and the solid was collected to give 1.85 g (73%) of **16**: mp 129–130 °C (EtOH–Et_2O); IR (Nujol) 1695 (C=O), 1650 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.33 (t, J = 7.5 Hz, 3, CH_2CH_3), 2.84 (s, 3, C2 CH_3), 4.32 (q, J = 7.5 Hz, 2, CH_2), 7.59 (t, J = 8 Hz, 1, C8 H), 7.89 (d, J = 8 Hz, 1, C9 H), 8.01 (d, J = 8 Hz, 1, C7 H), 9.02 (s, 3, C4 H); MS (EI) m/e 256 (M^+). Anal. ($C_{14}H_{12}N_2O_3$) C, H, N.

8-(Formylamino)-1,4-dihydro-4-oxo-2-quinolinecarboxylic Acid (17). A mixture of **8** (2.00 g, 8.76 mmol) and 35 mL of 1 N NaOH was stirred for 15 min and the resulting soltuion was treated with 35 mL of 1 N HCl. The resulting yellow precipitate was collected, washed with water, and dried to give 1.76 g (86%) of **17**: mp >272 °C; IR (Nujol) 3350–2500 (br stretching, spikes at 3310 and 3250), 1730 (C=O), 1670 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.70–7.42 (m, 2, aromatic), 7.90 (d, J = 8 Hz, 1, C7 H), 8.67 (s, 1, CHO), 8.70 (d, J = 8 Hz, 1, C5 H), 11.02 (br s, 1, NH); MS (CI) 233 ($M^+ + 1$), 261 ($M^+ + 29$), 273 ($M^+ + 41$). Anal. ($C_{11}H_8N_2O_4$) C, H, N.

8-(Formylamino)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (18). A mixture of **15a** (1.00 g, 4.13 mmol) and 25 mL of 1 N NaOH was stirred for several minutes. Solution did not occur, but the nature of the solid changed. The mixture was acidified with 1 N HCl and the resulting solid was collected, washed with water, and dried to give 0.918 g (96%) of **18**: mp >300 °C (dioxane–H_2O); IR (Nujol) 3450–2600 (br stretching, spike at 3310), 1640 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.27 (t, J = 8 Hz, 1, C6 H), 8.03–7.80 (m, 2, C5 H and C7 H), 8.33 (s, 1, CHO), 9.82 (br s, 1, NH), 10.03 (s, 1, C2 H), 10.85 (br s, 1, NH); MS (CI) 233 ($M^+ + 1$), 261 ($M^+ + 29$), 273 ($M^+ + 41$). Anal. ($C_{11}H_8N_2O_4$) C, H, N.

8-(Formylamino)-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (19). A solution of **15a** (1.20 g, 4.95 mmol) in 30 mL of HOAc containing a few milligrams of HOTs was heated at reflux for 3 h. The solution was concentrated and partitioned between CH_2Cl_2 and H_2O. The organic phase was dried (Na_2SO_4) and concentrated and the resulting red solid was recrystallized (EtOH) to give 0.950 g (74%) of **19**: mp 156–159 °C; IR (Nujol) 3350 (NH), 3320 (NH), 1690 (C=O), 1660 (C=O) cm^{-1}; MS (CI) 261 ($M^+ + 1$), 289 ($M^+ + 29$), 301 ($M^+ + 41$). Anal. ($C_{13}H_{12}N_2O_4$) C, H, N.

Biological Test Procedures. The PCA test used in these studies is similar to that described by Goose and Blair.[12] The backs of anesthetized (sodium pentobarbital) male Sprague–Dawley rats were shaven prior to receiving 100-μL injections of two dilutions of an homologous antiserum rich in IgE antiovalbumin antibodies. The two dilutions were prepared to yield average reaction diameters of 7 and 14 mm in control animals. Forty-eight to 72 hours later, the rats received test compound by intraperitoneal (ip) injection (60 mg/kg, prepared in 50% polyglycol E-200:50% water, v:v) or oral (po) gavage (100 mg/kg, prepared in 20% ethanol:80% water, v:v). The rats were challenged intravenously with 0.1 mg of ovalbumin and 2.5 mg of Evans blue dye contained in 0.5 mL of saline 5 min after ip or 30 min after po compound administration. Thirty minutes after challenge, the rats were sacrificed, the dorsal skin was reflected, and the mean reaction diameters were determined from measurements of two perpendicular axes. The sum of the two mean diameters determined the score for each animal. A minimum of four animals was used for both treatment and vehicle control groups, but results from repeated trials were pooled, causing both treatment and control n values to range from 4 to 12. Percent inhibition was calculated on the basis of difference in scores between control and treated animals and reported as mean percent inhibition plus or minus the standard error.

Weight changes in treated and control animals were monitored over a 2-week period, in experiments designed to assess potential toxicity problems with these compounds. Male Sprague–Dawley rats were fasted for 16 h prior to receiving a single oral dose of test compound (200 mg/kg, prepared in 0.1% Methocel) or control vehicle (0.1% Methocel). Each test group consisted of 8–10 animals, and their weights were obtained at approximately the same time every day. Weight changes were compared to the expected weight gain over the same time period based on standard growth charts for that age and strain of animal. (A negative number indicates an actual weight loss, while any number less than 100 indicates a failure to thrive, i.e., gain at the normal rate.) Mean percent of normal weight gain plus standard error was then calculated for each group. Means of data from both the PCA and weight gain experiments were compared by use of the two-tailed Student's t test, with $p < 0.05$ chosen as the level of statistical significance.

Registry No. **2**, 88-74-4; **3**, 762-42-5; **4**, 17454-33-0; **5**, 16134-01-3; **6**, 94110-83-5; **8**, 94110-84-6; **9**, 94110-85-7; **10**, 89-62-3; **11**, 87-13-8; **12a**, 7255-58-5; **12b**, 94110-93-7; **13a**, 94110-86-8; **13b**, 94110-94-8; **14a**, 94110-87-9; **14b**, 94110-95-9; **15a**, 94110-88-0; **15b**, 94110-96-0; **16**, 94110-89-1; **17**, 94110-90-4; **18**, 94110-91-5; **19**, 94110-92-6; triethyl orthoformate, 122-51-0; triethyl orthoacetate, 78-39-7.