# Quinolone Analogues 1. A Convenient Synthesis of 1-Alkyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylic Acids



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**Dedicated to the memory of Professor Raymond N. Castle**

The reaction of the alkylhydrazinoquinoxaline *N*-oxides **2a-d** with dimethyl acetylenedicarboxylate gave the dimethyl 1-alkyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **3a-d**, whose reaction with nitrous acid effected the $C_4$-oxidation to afford the dimethyl 1-alkyl-4-hydroxy-1,4-dihydropyridazino-[3,4-*b*]quinoxaline-3,4-dicarboxylates **4a-d**, respectively. The reaction of compounds **4a-d** with 1,8-diazabicyclo[5.4.0]-7-undecene in ethanol provided the ethyl 1-alkyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylates **5a-d**, while the reaction of compounds **4a-d** with potassium hydroxide furnished the 1-alkyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylic acids **6a-d**, respectively. Compounds **6c,d** were also obtained by the reaction of compounds **5c,d** with potassium hydroxide, respectively.

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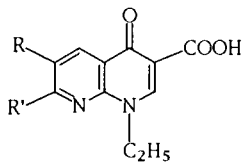
Since the discovery of nalidixic acid (Chart 1) in 1962 [1] and its introduction in the treatment of urinary tract infections in 1963, many research groups have developed a new class of quinolone antibacterials [2] including enoxacin [3], oxolinic acid [2], resoxacin [2], pipemidic acid [2], ofloxacin [4], and some other new quinolones [2]. Cinoxacin [2,5] and pyrimido[4,5-*c*]-pyridazines [2,6] possessing a pyridazine moiety have also been developed as analogues of nalidixic acid, while the pyrido[2,3-*b*]quinoxaline-3-carboxylic acids (Chart 2) have been synthesized and found to have bactericidal activity [7]. Hereupon, the structural hybridization of nalidixic acid, cinoxacin, and pyrido[2,3-*b*]quinoxaline-3-carboxylic acids provided

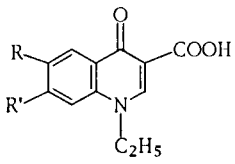
Chart 1

1,8-Naphthyridine



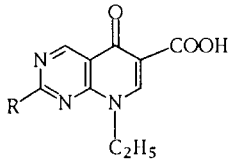
Nalidixic Acid
R = H, R' = $CH_3$
Enoxacin
R = F, R' = 1-Piperazinyl

Quinolone



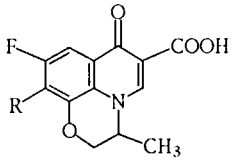
Oxolinic Acid
R, R' = $OCH_2O$
Resoxacin
R = H, R' = 4-Pyridyl

Pyrido[2,3-*d*]pyrimidine



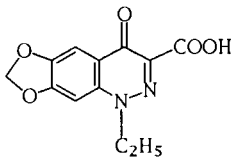
Pipemidic Acid
R = 1-Piperazinyl

Pyrido[1,2,3-*de*][1,4]benzoxazine



Ofloxacin
R = 4-Methyl-1-piperazinyl

Cinnoline



Cinoxacin

Pyrimido[4,5-*c*]pyridazine

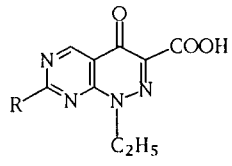
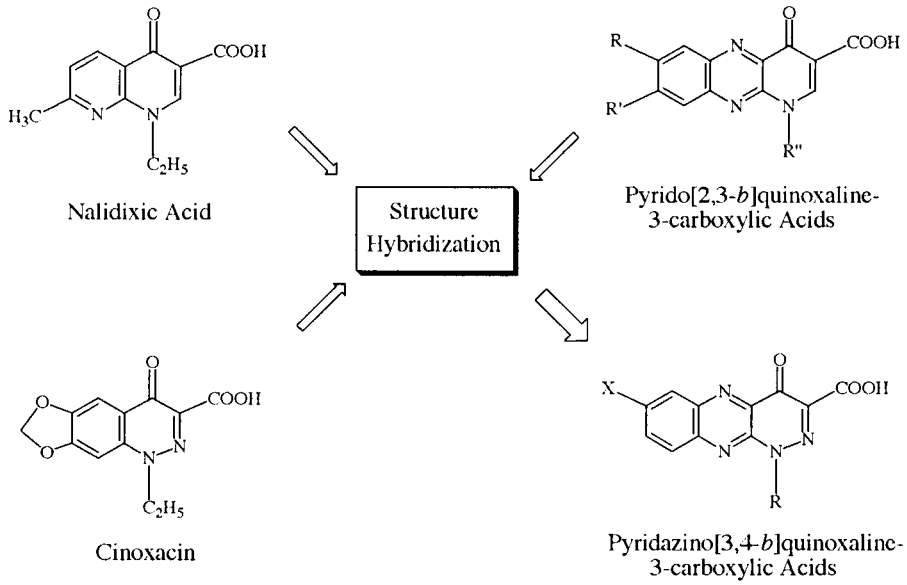
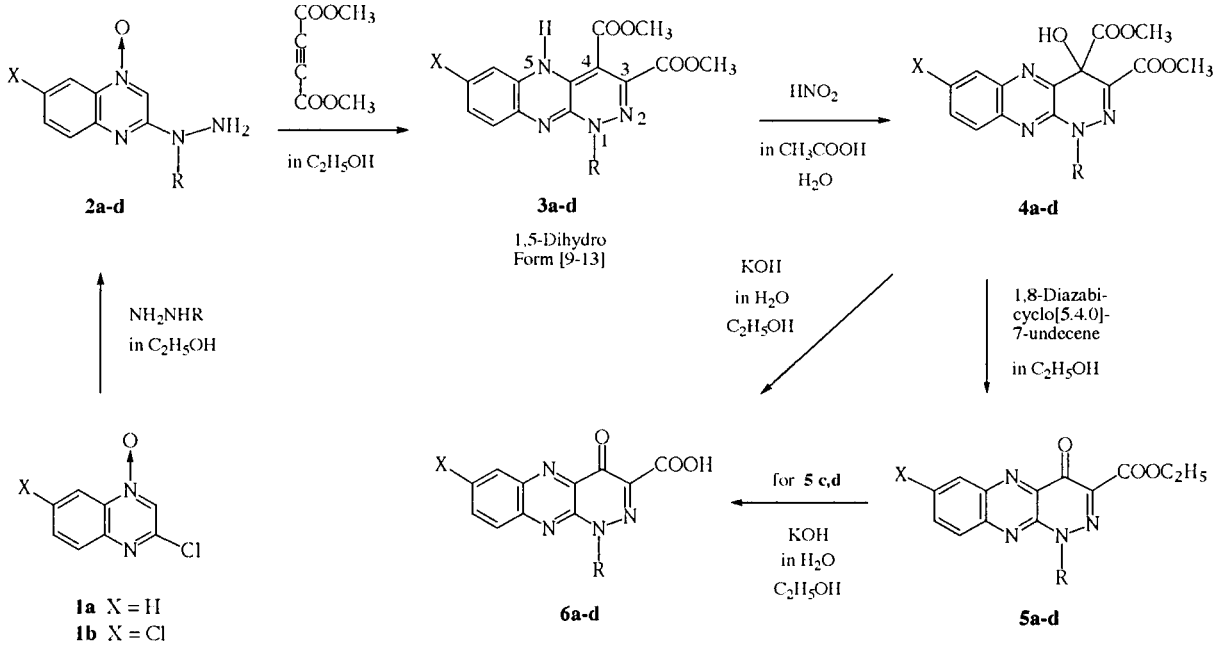


Chart 2



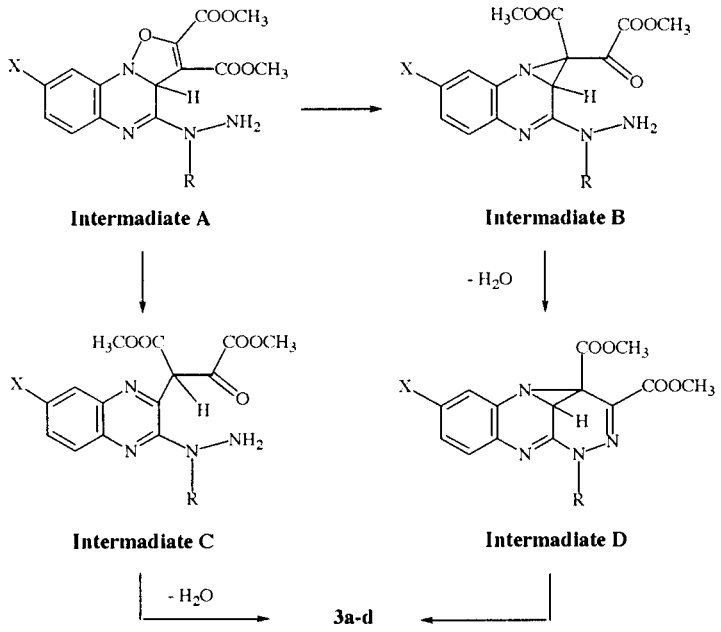

the pyridazino[3,4-*b*]quinoxaline-3-carboxylic acids (Chart 2) which have not been synthesized yet. In continuation of our investigation on pyridazine synthesis, we found a convenient and new method for the synthesis of the pyridazino[3,4-*b*]quinoxaline-3-carboxylic acids **6** and their esters **5** as shown in Scheme 1. Namely, our method initially constructs the pyridazine ring to obtain 1-alkylpyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **3** from quinoxaline *N*-oxides **2** [8], and then the pyridazine moiety of compounds **3** was converted into the 4-pyridazinone moiety of the pyridazino[3,4-*b*]quinoxaline-3-carboxylic acids **6** *via* a facile $C_4$-oxidation of compounds **3**, although a stepwise construction of a 4-pyridone or 4-pyridazinone moiety has been adopted for the synthesis of ordinary quinolones and new quinolones [2,7]. This paper describes a convenient method for the synthesis of the pyridazino[3,4-*b*]quinoxaline-3-carboxylic acids **6** and ethyl pyridazino[3,4-*b*]quinoxaline-3-carboxylates **5** (Scheme 1).

Scheme 1



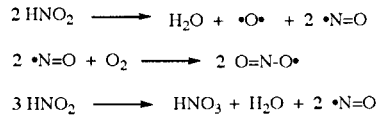

**2a-d - 6a-d**: **a** - X = H, R = $C_2H_5$; **b** - X = H, R = $CH_3$; **c** - X = Cl, R = $C_2H_5$; **d** - X = Cl, R = $CH_3$

Scheme 2




Concerning the oxidation of compounds **3a-d** to the $C_4$-hydroxy derivatives **4a-d**, we speculate a reaction mechanism as shown in Chart 3. Since nitrous acid has been known to generate nascent oxygen in an oxidation reaction (Scheme 3), the reaction of the 1,5-dihydropyridazino[3,4-*b*]quinoxalines **3a-d** with nascent oxygen would produce the $C_4$-hydroxy derivatives **4a-d** in an alternative mechanism A, B, or C (Chart 3).

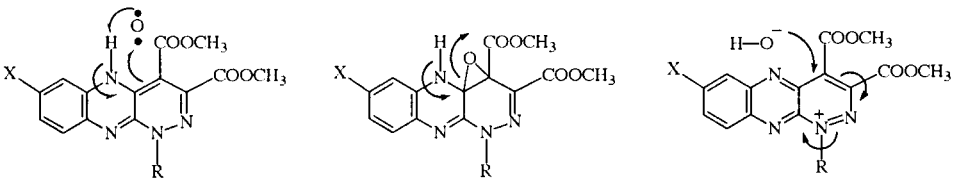
Scheme 3




Decomposition of $HNO_2$

Moreover, regarding the conversion of the $C_4$-hydroxy derivatives **4a-d** into the $C_4$-oxo derivatives **5a-d**, the abstraction of the $C_4$-hydroxy proton with a base would promote the elimination of methyl formate (Scheme 4). Since the reaction of the $C_4$-hydroxy derivative **4d** with 1,8-diazabicyclo[5.4.0]-7-undecene in ethanol gives the $C_4$-oxo derivative **5d** in similar yields both under aerobic

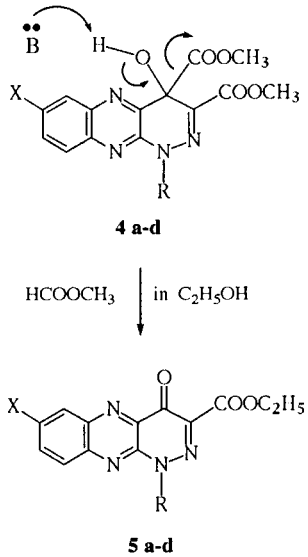
Chart 3



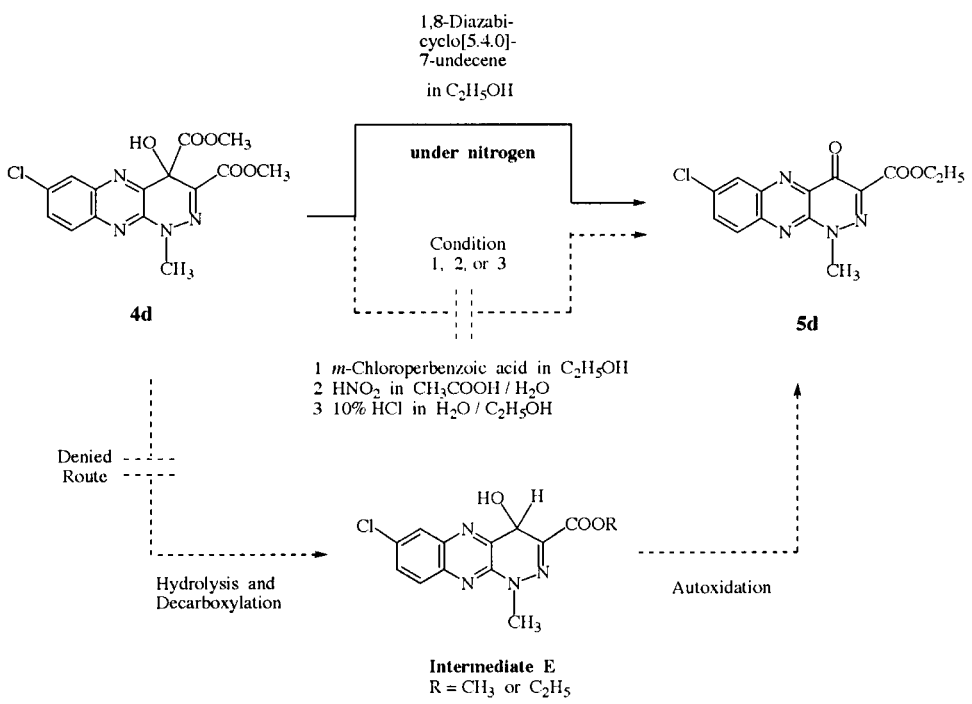
Postulated Oxidation Mechanism A Postulated Oxidation Mechanism B Postulated Oxidation Mechanism C

The reaction of quinoxaline *N*-oxides **1a** and **1b** with ethylhydrazine and methylhydrazine gave alkylhydrazinoquinoxaline *N*-oxides **2a-d** [8] (Scheme 1). The 1,3-dipolar cycloaddition reaction of compounds **2a-d** with dimethyl acetylenedicarboxylate afforded dimethyl 1-alkyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **3a-d** [8], respectively, *via* intermediates **A-D** (Scheme 2) [8]. Compound **3d** has already been reported to exist as the 1,5-dihydro form in our previous papers [9-13]. The reaction of compounds **3a-d** with nitrous acid effected the $C_4$-oxidation to provide dimethyl 1-alkyl-4-hydroxy-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **4a-d**, respectively. The reaction of compounds **4a-d** with 1,8-diazabicyclo[5.4.0]-7-undecene in ethanol resulted in both elimination of methyl formate and solvolysis to give ethyl 1-alkyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylates **5a-d**, respectively. The reaction of compounds **4a-d** with potassium hydroxide afforded 1-alkyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylic acids **6a-d**, respectively. Compounds **6c,d** were also obtained by the reaction of compounds **5c,d** with potassium hydroxide, respectively.

Scheme 4

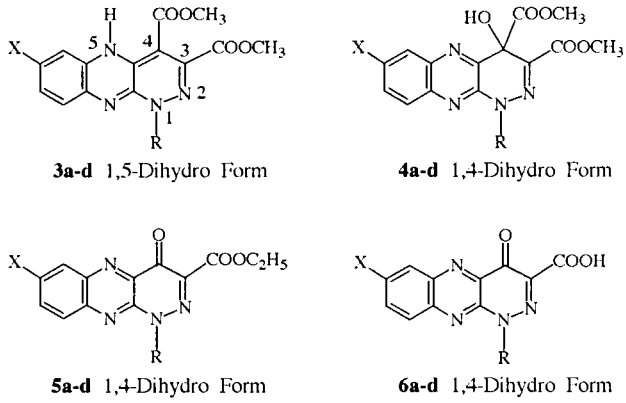


Scheme 5




condition (83%, see experimental section) and under nitrogen (79%), we deny a mechanism *via* an intermediate **E** which is to be produced by the hydrolysis and subsequent decarboxylation of the $C_4$-hydroxy derivative **4d** (Scheme 5). On the other hand, the reaction of the $C_4$-hydroxy derivative **4d** with an oxidizing agent such as *m*-chloroperbenzoic acid or nitrous acid under heating did not afford the $C_4$-oxo derivative **5d**, and an attempted hydrolysis of compound **4d** with 10% hydrochloric acid under heating also did not provide compound **5d** (Scheme 5).

Chart 4




Chemical Shift (δ ppm)

| Compound | Aromatic | $N_5$ - H | $C_4$ - OH |
|---|---|---|---|
| **3a-d** | 7.20 - 6.69 | 10.32 - 9.90 | ——— |
| **4a-d** | 8.10 - 7.72 | ——— | 7.15 - 7.06 |
| **5a-d** | 8.32 - 7.95 | ——— | ——— |
| **6a-d** | 8.42 - 7.94 | ——— | ——— |

The structural assignment of the above new compounds was based on analytical and spectral data. Especially, the structural change of compounds **3a-d** with the 1,5-dihydro form [9-11] into compounds **4a-d** with the 1,4-dihydro form was supported by the alteration of the chemical shifts for the aromatic protons. Namely, the aromatic protons of compounds **4a-d** (δ 8.10-7.72 ppm) were observed in lower magnetic fields than those of compounds **3a-d** (δ 7.20-6.69 ppm) (Chart 4). The $N_5$-H proton signals of compounds **3a-d** and the $C_4$-OH proton signals of compounds **4a-d** were observed at δ 10.32-9.90 and 7.15-7.06 ppm, respectively. The aromatic proton signals of compounds **5a-d** (δ 8.32-7.95 ppm) and **6a-d** (δ 8.42-7.94 ppm) with the 1,4-dihydro form were observed in similar magnetic fields to those of compounds **4a-d**.

## EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO FT/IR-200 spectrometer. The nmr spectra were measured with a Varian XL-400 spectrometer at 400 MHz. The chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL

JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

The synthesis of compounds **2d** and **3d** has already been reported by us [8].

3-(1-Ethylhydrazino)quinoxaline 1-Oxide (**2a**).

A solution of 3-chloroquinoxaline 1-oxide (10 g, 55.4 mmoles), ethylhydrazine (92% purity, 5.42 g, 83.1 mmoles), and triethylamine (5 ml) in ethanol (100 ml) was refluxed on a boiling water bath for 1 hour. The solution was allowed to stand overnight at room temperature to precipitate yellow needles of compound **2a**, which were collected by suction filtration and washed with *n*-hexane to give an analytically pure sample (9.86 g, 87%), mp 188-189°; ir ν $cm^{-1}$ 3340, 3120, 3075; 1610; ms: m/z 204 ($M^+$); pmr (deuteriodimethyl sulfoxide): 8.58 (s, 1H, $C_2$-H), 8.18 (dd, J = 1.5, 8.0 Hz, 1H, aromatic), 7.62 (ddd, J = 1.5, 8.0, 8.0 Hz, 1H, aromatic), 7.57 (dd, J = 2.0, 8.0 Hz, 1H, aromatic), 7.32 (ddd, J = 2.0, 8.0, 8.0 Hz, 1H, aromatic), 4.85 (s, 2H, $NH_2$), 3.78 (q, J = 7.0 Hz, 2H, $CH_2$), 1.17 (t, J = 7.0 Hz, 3H, $CH_3$).

*Anal.* Calcd. for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27,43. Found: C, 58.78; H, 5.92; N, 27.45.

3-(1-Methylhydrazino)quinoxaline 1-Oxide (**2b**).

A solution of 3-chloroquinoxaline 1-oxide (10 g, 55.4 mmoles) and methylhydrazine (10 g, 55.4 mmoles) in ethanol (150 ml) was refluxed on a boiling water bath for 1 hour. The solution was allowed to stand overnight at room temperation to precipitate yellow needles of compound **2b**, which were collected by suction filtration and washed with ethanol/*n*-hexane (1:1) to give an analytically pure sample (7.05 g). Evaporation of the filtrate *in vacuo* gave crystals, whose recrystallization from ethanol/water gave yellow needles of compound **2b** (2.13 g), total yield, 9.18 g (87%), mp 185-186°; ir ν $cm^{-1}$ 3330, 3120, 3070, 1620; ms: m/z 190 ($M^+$); pmr (deuteriodimethyl sulfoxide): 8.58 (s, 1H, $C_2$-H), 8.18 (dd, J = 1.5, 8.0 Hz, 1H, aromatic), 7.61 (ddd, J = 1.5, 8.0, 8.0 Hz, 1H, aromatic), 7.57 (dd, J = 2.0, 8.0 Hz, 1H, aromatic), 7.32 (ddd, J = 2.0, 8.0, 8.0 Hz, 1H, aromatic), 4.98 (s, 2H, $NH_2$), 3.30 (s, 3H, $CH_3$).

*Anal.* Calcd. for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.83; H, 5.23; N, 29.62.

6-Chloro-2-(1-ethylhydrazino)quinoxaline 4-Oxide (**2c**).

A solution of 2,6-dichloroquinoxaline 4-oxide (20 g, 93.0 mmoles), ethylhydrazine (92% purity, 10.92 g, 167.4 mmoles), and pyridine (20 ml) in chloroform (300 ml) was refluxed on a boiling water bath for 5 hours. Evaporation of the solvent *in vacuo* gave yellow crystals of compound **2c**, which were triturated with ethanol/water and then collected by suction filtration (13.79 g, 62%). Recrystallization from ethanol gave yellow needles, mp 177-178°; ir: ν $cm^{-1}$ 3340, 3120, 1610; ms: m/z 238 ($M^+$), 240 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 8.59 (s, 1H, $C_3$-H), 8.14 (dd, J = 2.0, 0.5 Hz, 1H, $C_5$-H), 7.63 (dd, J = 9.0, 2.0 Hz, 1H, $C_7$-H), 7.58 (dd, J = 0.5, 9.0 Hz, 1H, $C_8$-H), 4.90 (s, 2H, $NH_2$), 3.78 (q, J = 7.0 Hz, 2H, $CH_2$), 1.17 (t, J = 7.0 Hz, 3H, $CH_3$).

*Anal.* Calcd. for $C_{10}H_{11}ClN_4O$: C, 50.32; H, 4.65; Cl, 14.85; N, 23.47. Found: C, 50.42; H, 4.67; Cl, 14.76; N, 23.57.

Dimethyl 1-Ethyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylate (**3a**).

A solution of compound **2a** (10 g, 49.0 mmoles) and dimethyl acetylenedicarboxylate (10.44 g, 73.5 mmoles) in ethanol (200 ml) was refluxed on a boiling water bath for 3 hours to precipitate yellow needles of compound **3a**, which were collected by suction filtration and washed with ethanol (12.33 g, 77%). Recrystallization from *N,N*-dimethylformamide/ethanol gave yellow needles, mp 170-171°; ir: ν $cm^{-1}$ 1730, 1650; ms: m/z 328 ($M^+$); pmr (deuteriodimethyl sulfoxide): 10.32 (brs, 1H, NH), 6.98 (dd, J = 1.5, 8.0 Hz, 1H, aromatic), 6.86-6.72 (m, 3H, aromatic), 3.70 (s, 3H, ester $CH_3$), 3.66 (s, 3H, ester $CH_3$), 3.59 (q, J = 7.0 Hz, 2H, $CH_2$), 1.11 (t, J = 7.0 Hz, 3H, $CH_3$).

*Anal.* Calcd. for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.31; H, 4.97; N, 16.91.

Dimethyl 1-Methyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylate (**3b**).

A solution of compound **2b** (10 g, 52.6 mmoles) and dimethyl acetylenedicarboxylate (11.20 g, 78.9 mmoles) in ethanol (200 ml) was refluxed on a boiling water bath for 3 hours to precipitate yellow needles of compound **3b**, which were collected by suction filtration (11.58 g, 70%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp 175-176°; ir: ν $cm^{-1}$ 1735, 1650; ms: m/z 314 ($M^+$); pmr (deuteriodimethyl sulfoxide): 10.30 (s, 1H, NH), 7.00 (ddd, J = 2.0, 1.0, 8.0 Hz, 1H, aromatic), 6.86-6.79 (m, 3H, aromatic), 3.69 (s, 3H, ester $CH_3$), 3.66 (s, 3H, ester $CH_3$), 3.12 (s, 3H, $N_1$-$CH_3$).

*Anal.* Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.15; H, 4.50; N, 17.59.

Dimethyl 7-Chloro-1-ethyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylate (**3c**).

A solution of compound **2c** (5 g, 21.0 mmoles) and dimethyl acetylenedicarboxylate (4.47 g, 31.5 mmoles) in ethanol (200 ml) was refluxed on a boiling water bath for 10 hours to precipitate orange needles of compound **3c**. The reaction mixture was allowed to stand overnight, and then the orange needles were collected by suction filtration (4.80 g, 63%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded orange needles, mp 194-195°; ir: ν $cm^{-1}$ 2955, 1735, 1670; ms: m/z 362 ($M^+$), 364 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 10.22 (s, 1H, NH), 7.19 (d, J = 2.0 Hz, 1H, $C_6$-H), 6.80 (dd, J = 8.5, 2.0 Hz, 1H, $C_8$-H), 6.69 (d, J = 8.5 Hz, 1H, $C_9$-H), 3.70 (s, 3H, ester $CH_3$), 3.67 (s, 3H, ester $CH_3$), 3.59 (q, J = 7.0 Hz, 2H, $CH_2$), 1.10 (t, J = 7.0 Hz, 3H, $CH_3$).

*Anal.* Calcd. for $C_{16}H_{15}ClN_4O_4$: C, 52.97; H, 4.17; Cl, 9.77; N, 15.44. Found: C, 53.05; H, 4.22; Cl, 9.86; N, 15.54.

Dimethyl 1-Ethyl-4-hydroxy-1,4-dihydropyridazino[3,4-*b*]-quinoxaline-3,4-dicarboxylate (**4a**).

A solution of sodium nitrite (5.26 g, 76.2 mmoles) in water (50 ml) was added dropwise to a suspension of compound **3a** (10 g, 30.5 mmoles) in acetic acid (200 ml) with stirring in an ice-water bath. Then, the reaction mixture was refluxed in an oil bath for 1 hour, wherein aspiration was carried out through a T tube attached to the top of the condenser. The solvent was evaporated *in vacuo* to give crystals of compound **4a**, which were triturated with ethanol/water and then collected by suction filtration (4.32 g). Evaporation of the filtrate *in vacuo* afforded an oily substance, whose crystallization from ethanol/water provided additional yellow crystals of compound **4a** (1.65 g), total yield, 5.97 g (57%). Recrystallization from ethanol/water gave yellow needles, mp 146-147°; ir: ν $cm^{-1}$ 3310, 1760, 1715; ms: m/z 344 ($M^+$); pmr (deuteriodimethyl sulfoxide): 8.10 (ddd, J = 8.0, 1.5, 1.0 Hz, 1H, aromatic), 7.98 (ddd, J = 8.0, 1.5, 1.0 Hz,

1H, aromatic), 7.85 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, aromatic), 7.72 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, aromatic), 7.06 (s, 1H, OH), 4.35 (q, J = 7.0 Hz, 2H, $CH_2$), 3.79 (s, 3H, ester $CH_3$), 3.67 (s, 3H, ester $CH_3$), 1.36 (t, J = 7.0 Hz, 3H, $CH_3$).

*Anal.* Calcd. for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.62; H, 4.70; N, 16.27.

Dimethyl 4-Hydroxy-1-methyl-1,4-dihydropyridazino[3,4-*b*]-quinoxaline-3,4-dicarboxylate (**4b**).

A solution of sodium nitrite (5.52 g, 80 mmoles) in water (50 ml) was added dropwise to a suspension of compound **3b** (10 g, 31.8 mmoles) in acetic acid (200 ml) with stirring in an ice-water bath. Then, the reaction mixture was refluxed in an oil bath for 1 hour, wherein aspiration was carried out through a T tube attached to the top of the condenser. The solvent was evaporated *in vacuo* to give crystals of compound **4b**, which were triturated with ethanol/water and then collected by suction filtration (4.95 g). Evaporation of the filtrate *in vacuo* afforded an oily substance, whose crystallization from ethanol/water provided additional yellow crystals of compound **4b** (1.22 g), total yield, 6.17 g (59%). Recrystallization from *N,N*-dimethylformamide/ethanol/water gave yellow prisms, mp 208-209°; ir: ν $cm^{-1}$ 3360, 1760, 1715; ms: m/z 330 ($M^+$); pmr (deuteriodimethyl sulfoxide): 8.02 (ddd, J = 8.0, 1.5, 1.0 Hz, 1H, aromatic), 7.99 (ddd, J = 8.0, 1.5, 1.0 Hz, 1H, aromatic), 7.85 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, aromatic), 7.72 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, aromatic), 7.06 (s, 1H, OH), 3.85 (s, 3H, $N_1$-$CH_3$), 3.78 (s, 3H, ester $CH_3$), 3.67 (s, 3H, ester $CH_3$).

*Anal.* Calcd. for $C_{15}H_{14}N_4O_5$: C, 54.55; H, 4.27; N, 16.94. Found: C, 54.49; H, 4.39; N, 16.94.

Dimethyl 7-Chloro-1-ethyl-4-hydroxy-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylate (**4c**).

A solution of sodium nitrite (0.86 g, 12.4 mmoles) in water (10 ml) was added dropwise to a suspension of compound **3c** (3 g, 8.28 mmoles) in acetic acid (90 ml)/water (10 ml) with stirring in an ice-water bath. The reaction mixture was refluxed in an oil bath for 1 hour, wherein aspiration was carried out through a T tube attached to the top of the condenser. Evaporation of the solvent *in vacuo* afforded yellow crystals of compound **4c**, which were triturated with ethanol/water and then collected by suction filtration (2.63 g, 84%). Recrystallization from ethanol afforded yellow prisms, mp 181-182°; ir: ν $cm^{-1}$ 1770, 1710; ms: m/z 378 ($M^+$), 380 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 8.09 (dd, J = 2.0, 0.5 Hz, 1H, $C_6$-H), 7.99 (dd, J = 9.0, 0.5 Hz, 1H, $C_9$-H), 7.87 (dd, J = 2.0, 9.0 Hz, 1H, $C_8$-H), 7.13 (s, 1H, OH), 4.33 (q, J = 7.0 Hz, 2H, $CH_2$), 3.79 (s, 3H, ester $CH_3$), 3.67 (s, 3H, ester $CH_3$), 1.35 (t, J = 7.0 Hz, 3H, $CH_3$).

*Anal.* Calcd. for $C_{16}H_{15}ClN_4O_5$: C, 50.74; H, 3.99; Cl, 9.36; N, 14.79. Found: C, 50.53; H, 4.01; Cl, 9.45; N, 14.77.

Dimethyl 7-Chloro-4-hydroxy-1-methyl-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylate (**4d**).

A solution of sodium nitrite (2.97 g, 43.0 mmoles) in water (30 ml) was added dropwise to a suspension of compound **3d** (10 g, 28.7 mmoles) in acetic acid (300 ml)/water (20 ml) with stirring in an ice-water bath. Then, the reaction mixture was refluxed in an oil bath for 1 hour, wherein aspiration was carried out through a T tube attached to the top of the condenser. Evaporation of the solvent *in vacuo* afforded yellow crystals of compound **4d**, which were triturated with ethanol/water and then collected by suction filtration (7.35 g, 70%). Recrystallization from ethanol provided yellow prisms, mp 254-255°; ir: ν $cm^{-1}$ 1764, 1712; ms: m/z 364 ($M^+$), 366 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 8.10 (dd, J = 2.5, 0.5 Hz, 1H, $C_6$-H), 8.01 (dd, J = 9.0, 0.5 Hz, 1H, $C_9$-H), 7.88 (dd, J = 2.5, 9.0 Hz, 1H, $C_8$-H), 7.15 (s, 1H, OH), 3.84 (s, 3H, $N_1$-$CH_3$), 3.79 (s, 3H, ester $CH_3$), 3.67 (s, 3H, ester $CH_3$).

*Anal.* Calcd. for $C_{15}H_{13}ClN_4O_5$: C, 49.39; H, 3.59; Cl, 9.72; N, 15.36. Found: C, 49.15; H, 3.73; Cl, 9.84; N, 15.22.

Ethyl 1-Ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylate (**5a**).

A solution of compound **4a** (2 g, 5.81 mmoles) and 1,8-diazabicyclo[5.4.0]-7-undecene (1.33 g, 8.75 mmoles) in ethanol (60 ml) was refluxed on a boiling water bath for 2 hours. After the reaction, acetic acid (5 ml) was added to the reaction mixture. The solvent was evaporated *in vacuo* to give an oily substance, which was dissolved in chloroform. The chloroform solution was washed with water, dried over anhydrous sodium sulfate, and then evaporated *in vacuo* to give brown crystals of compound **5a** (0.93 g, 54%). Recrystallization from ethanol/*n*-hexane afforded yellow needles, mp 128-129°; ir: ν $cm^{-1}$ 1725, 1665, 1645; ms: m/z 298 ($M^+$); pmr (deuteriodimethyl sulfoxide): 8.28 (ddd, J = 8.5, 1.5, 1.0 Hz, 1H, aromatic), 8.13 (ddd, J = 8.5, 1.5, 1.0 Hz, 1H, aromatic), 8.06 (ddd, J = 8.5, 8.5, 1.5 Hz, 1H, aromatic), 7.95 (ddd, J = 8.5, 8.5, 1.5 Hz, 1H, aromatic), 4.68 (q, J = 7.0 Hz, 2H, $CH_2$), 4.35 (q, J = 7.0 Hz, 2H, $CH_2$), 1.47 (t, J = 7.0 Hz, 3H, $CH_3$), 1.32 (t, J = 7.0 Hz, 3H, $CH_3$).

*Anal.* Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.21; H, 4.81; N, 18.76.

Ethyl 1-Methyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylate (**5b**).

A solution of compound **4b** (2 g, 6.06 mmoles) and 1,8-diazabicyclo[5.4.0]-7-undecene (1.38 g, 9.09 mmoles) in ethanol (60 ml) was refluxed on a boiling water bath for 2 hours. The solution was allowed to stand overnight at room temperature to precipitate brown needles of compound **5b**, which were collected by suction filtration and washed with ethanol and then *n*-hexane to give an analytically pure sample (0.95 g, 55%), mp 185-186°; ir: ν $cm^{-1}$ 1750, 1730, 1655, 1645; ms: m/z 284 ($M^+$); pmr (deuteriodimethyl sulfoxide): 8.32 (ddd, J = 8.5, 1.5, 1.0 Hz, 1H, aromatic), 8.17 (ddd, J = 8.5, 1.5, 1.0 Hz, 1H, aromatic), 8.09 (ddd, J = 8.5, 8.5, 1.5 Hz, 1H, aromatic), 7.98 (ddd, J = 8.5, 8.5, 1.5 Hz, 1H, aromatic), 4.35 (q, J = 7.0 Hz, 2H, $CH_2$), 4.19 (s, 3H, $N_1$-$CH_3$), 1.32 (t, J = 7.0 Hz, 3H, $CH_3$).

*Anal.* Calcd. for $C_{14}H_{12}N_4O_4$: C, 59.15; H, 4.25; N, 19.71. Found: C, 58.90; H, 4.37; N, 19.82.

Ethyl 7-Chloro-1-ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]-quinoxaline-3-carboxylate (**5c**).

A solution of compound **4c** (2 g, 5.28 mmoles) and 1,8-diazabicyclo[5.4.0]-7-undecene (1.20 g, 7.92 mmoles) in ethanol (100 ml) was refluxed on a boiling water bath for 2 hours. After the reaction, acetic acid (5 ml) was added to the reaction mixture. Evaporation of the solvent *in vacuo* gave brown crystals of compound **5c**, which were triturated with water and then collected by suction filtration (1.48 g, 84%). Recrystallization from ethanol/water provided brown prisms, mp 206-207°; ir: ν $cm^{-1}$ 1730, 1655; ms: m/z 332 ($M^+$), 334 ($M^+$ + 2); pmr (deuteriotrifluoroacetic acid): 8.23 (d, J = 2.0 Hz, 1H, $C_6$-H), 8.16 (d, J =

9.0 Hz, 1H, $C_9$-H), 7.98 (dd, J = 2.0, 9.0 Hz, 1H, $C_8$-H), 5.03 (q, J = 7.0 Hz, 2H, $CH_2$), 4.52 (q, J = 7.0 Hz, 2H, $CH_2$), 1.56 (t, J = 7.0 Hz, 3H, $CH_3$), 1.34 (t, J = 7.0 Hz, 3H, $CH_3$).

*Anal.* Calcd. for $C_{15}H_{13}ClN_4O_3$: C, 54.14; H, 3.94; Cl, 10.65; N, 16.84. Found: C, 54.19; H, 4.16; Cl, 10.51; N, 17.13.

Ethyl 7-Chloro-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]-quinoxaline-3-carboxylate (**5d**).

A solution of compound **4d** (5 g, 13.7 mmoles) and 1,8-diazabicyclo[5.4.0]-7-undecene (3.13 g, 20.6 mmoles) in ethanol (200 ml) was refluxed on a boiling water bath for 2 hours. After the reaction, acetic acid (5 ml) was added to the reaction mixture. Evaporation of the solvent *in vacuo* gave brown crystals of compound **5d**, which were triturated with water and then collected by suction filtration (3.62 g, 83%). Recrystallization from ethanol/water afforded brown needles, mp 228-229°; ir: ν $cm^{-1}$ 1725, 1658; ms: m/z 318 ($M^+$), 320 ($M^+$ + 2); pmr (deuteriotrifluoroacetic acid): 8.17 (d, J = 2.0 Hz, 1H, $C_6$-H), 8.15 (d, J = 9.5 Hz, 1H, $C_9$-H), 7.95 (dd, J = 2.0, 9.5 Hz, 1H, $C_8$-H), 4.48 (q, J = 7.0 Hz, 2H, $CH_2$), 4.47 (s, 3H, $N_1$-$CH_3$), 1.31 (t, J = 7.0 Hz, 3H, $CH_3$).

*Anal.* Calcd. for $C_{14}H_{11}ClN_4O_3$: C, 52.76; H, 3.48; Cl, 11.12; N, 17.58. Found: C, 52.62; H, 3.69; Cl, 11.20; N, 17.70.

1-Ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylic Acid (**6a**).

A solution of compound **4a** (2 g, 6.37 mmoles) and potassium hydroxide (0.71 g, 12.7 mmoles) in ethanol (80 ml)/water (20 ml) was refluxed on a boiling water bath for 2 hours to precipitate crystals. After the reaction, addition of 1*N* hydrochloric acid (15 ml) to the reaction mixture with stirring gave a clear solution. Evaporation of the solvent *in vacuo* to a small volume afforded brown needles of compound **6a**, which were collected by suction filtration and washed with water to provide an analytically pure sample (1.47 g, 85%), mp 283-284°; ir: ν $cm^{-1}$ 1760, 1600; ms: m/z 270 ($M^+$); pmr (deuteriotrifluoroacetic acid): 8.22 (dd, J = 8.0, 1.5 Hz, 1H, aromatic), 8.21 (dd, J = 8.0, 1.5 Hz, 1H, aromatic), 8.07 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, aromatic), 7.99 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, aromatic), 5.05 (q, J = 7.0 Hz, 2H, $CH_2$), 1.55 (t, J = 7.0 Hz, 3H, $CH_3$). The COOH proton signal was not observed because of D-H exchange.

*Anal.* Calcd. for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.73; N, 20.73. Found: C, 57.59; H, 3.78; N, 20.73.

1-Methyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylic Acid (**6b**).

A solution of compound **4b** (2 g, 6.06 mmoles) and potassium hydroxide (0.68 g, 12.1 mmoles) in ethanol (80 ml)/water (20 ml) was refluxed on a boiling water bath for 2 hours. Cooling of the solution to room temperature precipitated crystals, and addition of 1*N* hydrochloric acid (13 ml) to the reaction mixture with stirring gave a clear solution. Evaporation of the solvent *in vacuo* to a small volume provided brown crystals of compound **6b**, which were collected by suction filtration and washed with water to afford an analytically pure sample (1.47 g, 95%), mp above 300°; ir: ν $cm^{-1}$ 1760, 1600; ms: m/z 256 ($M^+$); pmr (deuteriotrifluoroacetic acid): 8.24 (dd, J = 8.0, 1.5 Hz, 1H, aromatic), 8.21 (dd, J = 8.0, 1.5 Hz, 1H, aromatic), 8.09 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, aromatic), 8.01 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, aromatic), 4.52 (s, 3H, $N_1$-$CH_3$). The COOH proton signal was not observed because of D-H exchange.

*Anal.* Calcd. for $C_{12}H_8N_4O_3$: C, 56.25; H, 3.15; N, 21.87. Found: C, 56.54; H, 3.32; N, 21.91.

7-Chloro-1-ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylic Acid (**6c**).

Method 1.

A solution of compound **4c** (1 g, 2.64 mmoles) and potassium hydroxide (296 mg, 5.28 mmoles) in ethanol (80 ml)/water (20 ml) was refluxed for 2 hours with stirring in an oil bath. After the reaction, 1*N* hydrochloric acid (8 ml) was added to the cooled reaction mixture, and evaporation of the solvent *in vacuo* gave brown crystals of compound **6c**, which were triturated with water and then collected by suction filtration (0.73 g, 91%). Recrystallization from dioxane/water provided brown prismic needles.

Method 2.

A solution of compound **5c** (1 g, 3.0 mmoles) and potassium hydroxide (252 mg, 4.5 mmoles) in ethanol (90 ml)/water (10 ml) was refluxed for 2 hours with stirring in an oil bath. After the reaction, 1*N* hydrochloric acid (5 ml) was added to the cooled reaction mixture, and evaporation of the solvent *in vacuo* gave brown crystals of compound **6c**, which were triturated with water and then collected by suction filtration (0.86 g, 94%). Recrystallization from dioxane/water provided brown prismic needles.

Compound **6c** had mp 220-221°; ir: ν $cm^{-1}$ 1740, 1725, 1650, 1605; ms: m/z 304 ($M^+$), 306 ($M^+$ + 2); pmr (deuteriodimethyl sulfoxide): 8.42 (d, J = 2.0 Hz, 1H, $C_6$-H), 8.16 (d, J = 9.5 Hz, 1H, $C_9$-H), 8.06 (dd, J = 2.0, 9.5 Hz, 1H, $C_8$-H), 4.69 (q, J = 7.0 Hz, 2H, $CH_2$), 1.47 (t, J = 7.0 Hz, 3H, $CH_3$). The COOH proton signal was not observed because of the presence of moisture in solution.

*Anal.* Calcd. for $C_{13}H_9ClN_4O_3$: C, 51.25; H, 2.98; Cl, 11.64; N, 18.39. Found: C, 51.14; H, 3.25; Cl, 11.73; N, 18.44.

7-Chloro-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylic Acid (**6d**).

Method 1.

A solution of compound **4d** (1 g, 2.74 mmoles) and potassium hydroxide (307 mg, 5.48 mmoles) in ethanol (80 ml)/water (20 ml) was refluxed for 2 hours with stirring in an oil bath. After the reaction, 1*N* hydrochloric acid (8 ml) was added to the cooled reaction mixture. Evaporation of the solvent *in vacuo* provided brown crystals of compound **6d**, which were triturated with water and then collected by suction filtration (0.66 g, 86%). Recrystallization from ethanol afforded brown prisms.

Method 2.

A suspension of compound **5d** (1 g, 3.14 mmoles) and potassium hydroxide (352 mg, 6.28 mmoles) in ethanol (80 ml)/water (20 ml) was refluxed for 2 hours with stirring in an oil bath to precipitate red crystals. After the reaction, 1*N* hydrochloric acid (8 ml) was added to the cooled reaction mixture to dissolve the above red crystals. Evaporation of the solvent *in vacuo* provided brown crystals of compound **6d**, which were triturated with water and then collected by suction filtration (0.77 g, 84%). Recrystallization from ethanol afforded brown prisms.

Compound **6d** had mp 304-305°; ir: ν $cm^{-1}$ 3062, 1750, 1600; ms: m/z 290 ($M^+$), 292 ($M^+$ + 2); pmr (deuteriotrifluoroacetic acid): 8.14 (d, J = 2.0 Hz, 1H, $C_6$-H), 8.12 (d, J = 10.0 Hz, 1H, $C_9$-H), 7.94 (dd, J = 2.0, 10.0 Hz, 1H, $C_8$-H), 4.47 (s, 3H,

$N_1$-$CH_3$). The COOH proton signal was not observed because of D-H exchange.

*Anal.* Calcd. for $C_{12}H_7ClN_4O_3$: C, 49.59; H, 2.43; Cl, 12.20; N, 19.28. Found: C, 49.65; H, 2.61; Cl, 12.15; N, 19.25.

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