Quinolone Analogues 2. A Facile Synthesis of Novel 3-Substituted 1-Alkyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalines

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The reaction of the 2-(1-alkylhydrazino)-6-chloroquinoxaline 4-oxides **1a,b** with diethyl acetonedicarboxylate or 1,3-cyclohexanedione gave ethyl 1-alkyl-7-chloro-3-ethoxycarbonylmethylene-1,5-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylates **5a,b** or 6-alkyl-10-chloro-1-oxo-1,2,3,4,6,12-hexahydroquinoxalino[2,3-*c*]cinnolines **7a,b**, respectively. Oxidation of compounds **5a,b** with nitrous acid afforded the ethyl 1-alkyl-7-chloro-3-ethoxycarbonylmethylene-4-hydroxy-1,4-dihydropyridazino-[3,4-*b*]quinoxaline-4-carboxylates **9a,b**, whose reaction with base provided the ethyl 2-(1-alkyl-7-chloro-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)acetates **6a,b**, respectively. On the other hand, oxidation of compounds **7a,b** with *N*-bromosuccinimide/water furnished the 4-(1-alkyl-7-chloro-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)butyric acids **8a,b**, respectively. The reaction of compound **8a** with hydroxylamine gave 4-(7-chloro-4-hydroxyimino-1-methyl-1,4-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)-butyric acid **12**.

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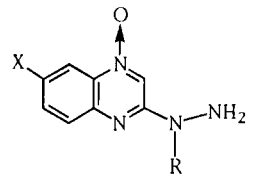
In a previous paper [1], we reported the synthesis of the 1-alkyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxylic acids **4** (Chart 1) from the alkylhydrazinoquinoxaline *N*-oxides **1** *via* the dimethyl 1-alkyl-1,5-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **2** and the dimethyl 1-alkyl-4-hydroxy-1,4-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylates **3**. Since our compounds **4** are regarded as analogues of nalidixic acid [2], cinoxacin [2,3], and pyrido[2,3-*b*]quinoxalines [4] (Chart 2) having antibacterial activity, compounds **4** were expected to possess excellent antibacterial activity. However, our screening data showed that compounds **4** were inferior to nalidixic acid or cinoxacin in the antibacterial activity. Accordingly, the structural modification of compounds **4** was necessary to produce more potent compounds. As an example for the modification of the C_3-substituent in quinolone analogues, 3-quinolinecarboxamide (Chart 2) has been known to possess the excellent antiherpetic activity [5]. This result indicates that the replacement of the C_3-carboxyl group with other functional group in quinolone analogues brings about a favorable effect on the biological activity, although the ordinary antibacterial quinolones require the carboxyl group at the C_3-position. Thus, we have planned the modification of the C_3-substituent as shown in Chart 3 which shows the structural change of compounds **4** into compounds **6** and **8** having the methylene chain between the C_3 carbon and the carboxyl (or its ester) group, and we have accomplished the synthesis of the 2-(1-alkyl-7-chloro-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)acetates **6** (Scheme 2) and 4-(1-alkyl-7-chloro-4-oxo-1,4-dihydropyridazino-[3,4-*b*]quinoxalin-3-yl)butyric acids **8** (Scheme 3) from compounds **1a,b** *via* the pyridazino[3,4-*b*]quinoxalines **5** and quinoxalino[2,3-*c*]cinnolines **7**, respectively. This paper describes the synthesis of novel pyridazino[3,4-*b*]-quinoxalines **5** and quinoxalino[2,3-*c*]cinnolines **7** (Scheme 1) together with the conversion of compounds **5** and **7** into new 1-alkyl-7-chloro-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalines **6**, **8**, and **11** possessing the methylene chain between the C_3 carbon and the carboxyl (or its ester) group.

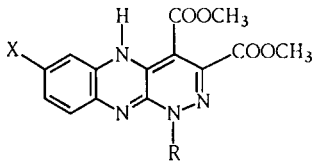
The reaction of the 2-(1-alkylhydrazino)-6-chloroquinoxaline 4-oxides **1a,b** with diethyl acetonedicarboxylate or 1,3-cyclohexanedione gave the ethyl 1-alkyl-7-chloro-3-ethoxycarbonylmethylene-1,5-dihydropyridazino[3,4-*b*]-quinoxaline-4-carboxylates **5a,b** or 6-alkyl-10-chloro-1-oxo-1,2,3,4,6,12-hexahydroquinoxalino[2,3-*c*]cinnolines **7a,b**, respectively (Scheme 1), presumably *via* a hydrazone intermediate **A** (Chart 4) [6].

The reaction of compound **5a** with nitrous acid resulted in C_4-hydroxylation [1] to afford ethyl 7-chloro-3-ethoxycarbonylmethylene-4-hydroxy-1-methyl-1,4-dihydropyridazino[3,4-*b*]quinoxaline-4-carboxylate **9a**, whose reaction with a base such as 1,8-diazabicyclo[5.4.0]-7-undecene or hydrazine hydrate in ethanol precipitated ethyl 2-(7-chloro-1-methyl-4-oxo-1,4-dihydropyridazino-[3,4-*b*]quinoxalin-3-yl)acetate **6a** (Scheme 2). The reaction of compound **5a** with nitrous acid did not produce the

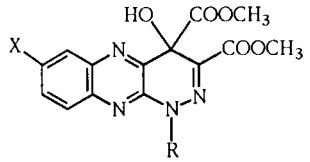
Chart 1



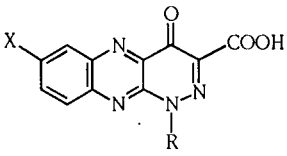
1 a-d



2 a-d

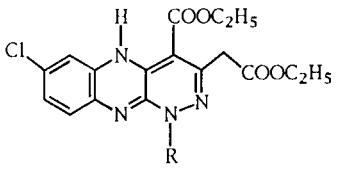


3 a-d

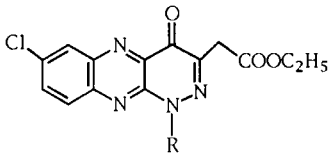


4 a-d

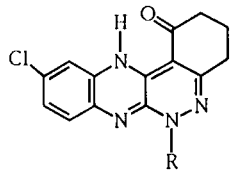
1 a-d - 4a-d : **a** - X = Cl, R = CH_3, **b** - X = Cl, R = C_2H_5, **c** - X = H, R = CH_3, **d** - X = H, R = C_2H_5



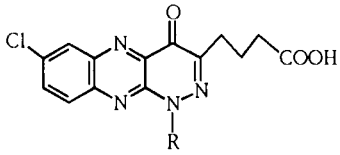
5 a,b



6 a,b



7 a,b



8 a,b

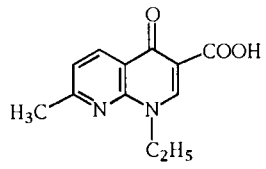
5 a,b - 8 a,b : **a** - R = CH_3, **b** - R = C_2H_5

oxime **10**, which was expected by the nitrosation of the active methylene group. On the other hand, the reaction of compound **5b** with *m*-chloroperbenzoic acid followed by the reaction with sodium carbonate provided ethyl 2-(7-chloro-1-ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]-quinoxalin-3-yl)acetate **6b** presumably *via* the C_4-hydroxy derivative **9b** which was not isolated.

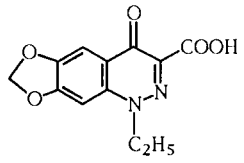
The reaction of compounds **7a,b** with *N*-bromosuccinimide/water resulted in oxidation to give the 4-(1-alkyl-7-chloro-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)butyric acids **8a,b** presumably *via* an intermediate **B** (Scheme 3). The esterification of compounds **8a,b** in concentrated sulfuric acid/ethanol afforded the ethyl 4-(1-alkyl-7-chloro-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)butyrates **11a,b**, respectively. The reaction of compound **8a** with hydroxylamine provided 4-(7-chloro-4-hydroxyimino-1-methyl-1,4-dihydropyridazino[3,4-*b*]-quinoxalin-3-yl)butyric acid **12**, whose reflux in concentrated sulfuric acid/ethanol furnished ethyl 4-(7-chloro-4-hydroxyimino-1-methyl-1,4-dihydropyridazino[3,4-*b*]-quinoxalin-3-yl)butyrate **13**. In this reaction, the Beckman rearrangement did not take place.

Concerning the C_4-hydroxylation of compounds **2** into compounds **3** (Chart 1) using nitrous acid in a previous paper [1], we have postulated a reaction mechanism A or B as shown in Chart 5, wherein nascent oxygen is generated by decomposition of nitrous acid (Scheme 4). The C_4-hydroxylation of compound **5a** to compound **9a** would also follow this mechanism A or B. On the other hand, when *m*-chloroperbenzoic acid is employed, the C_4-hydroxylation of compound **5b** to compound **9b** may be explained by a mechanism B (Chart 5) or mechanism C (Chart 6). The epoxidation of a C=C bond with *m*-chloroperbenzoic acid (mechanism B) has widely been

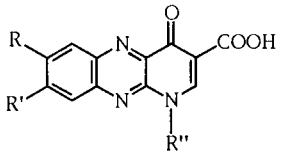
Chart 2



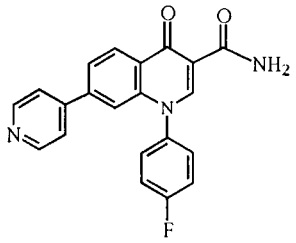
Nalidixic Acid



Cinoxacin

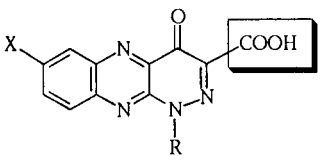


Pyrido[2,3-*b*]quinoxalines



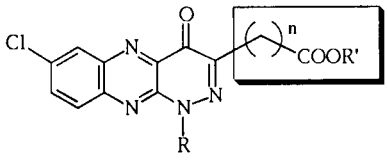
3-Quinolinecarboxamide

Chart 3



4 a-d

Modification of C_3-Substituent



6 a,b n = 1
8 a,b n = 3

Scheme 1

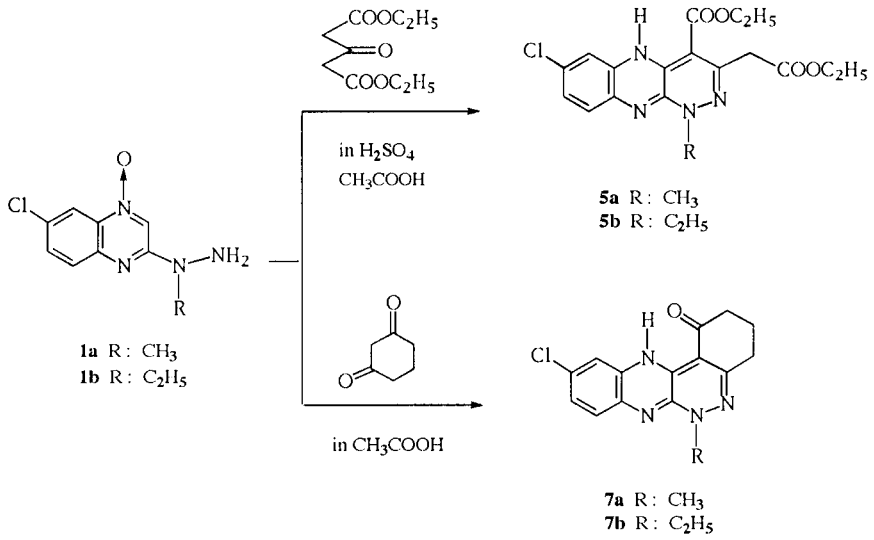
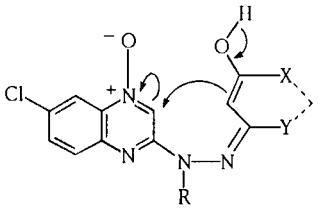


Chart 4



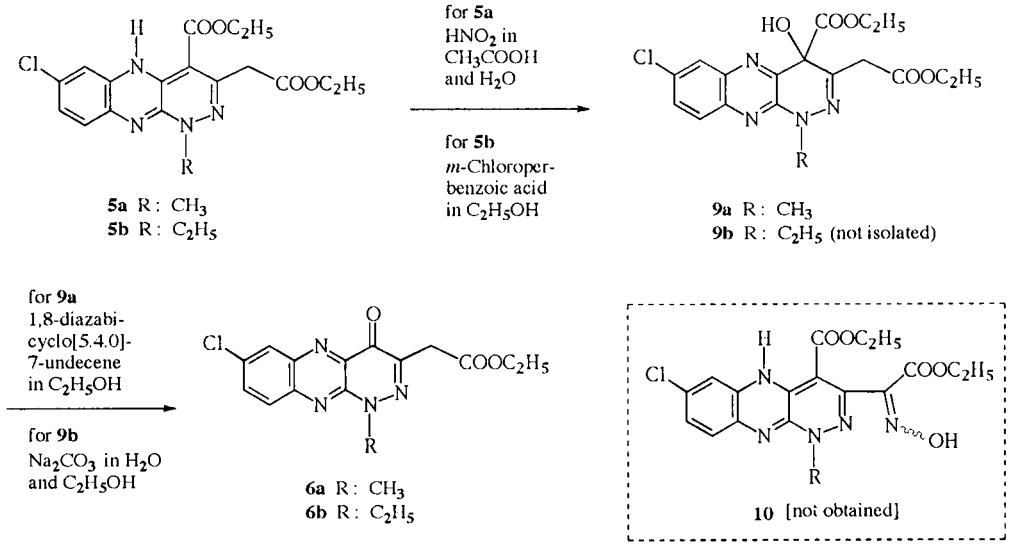
Hydrazone Intermediate **A**

known, and the hydroxylation of an enamino moiety with *m*-chloroperbenzoic acid (mechanism C) has already been reported by us [7,8]. In a similar mechanism to the above, compounds **8a,b** would be produced from compounds **7a,b** *via* an intermediate **B** as shown in Scheme 3.

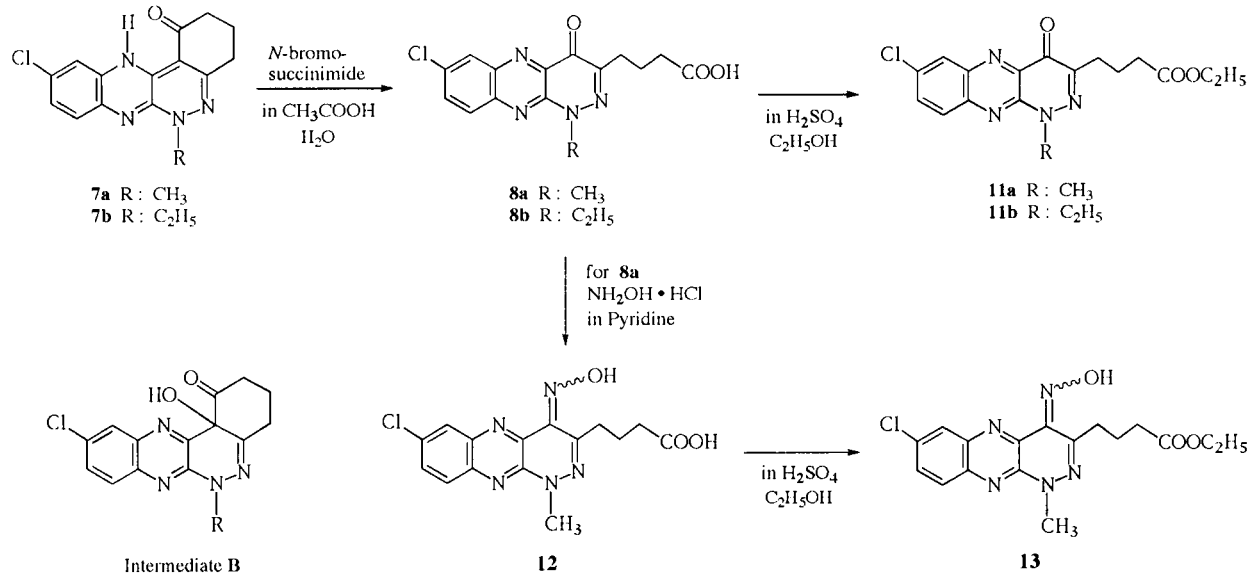
The conversion of compounds **9a,b** into compounds **6a,b** would be due to the elimination of formate, which is initiated by the deprotonation of the C_4-hydroxyl group with a base (Scheme 5) [1].

The structural assignment of above new compounds was based on the analytical and spectral data. For example, the aromatic proton signals of compound **5a** (δ 7.10 - 6.67 ppm) with the 1,5-dihydro form were observed in higher magnetic fields than those of compounds **9a** (δ 8.00 - 7.76 ppm) and **6a** (δ 8.06 - 7.81 ppm) with the 1,4-dihydro form (Chart 7) [1]. This tendency was also observed between compound **7a** (aromatic protons, δ 7.23 - 6.77 ppm) and compound **11a** (aromatic protons, δ 8.33 - 7.99 ppm) (Chart 7). The C=O carbon signals assigned by the HMBC and HMQC spectral data are also shown in Chart 7. The

Scheme 2



Scheme 3



7a R: CH_3
7b R: C_2H_5

8a R: CH_3
8b R: C_2H_5

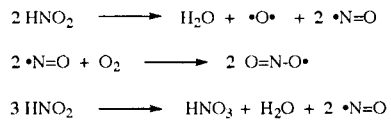
11a R: CH_3
11b R: C_2H_5

Intermediate B

12

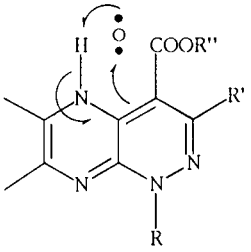
13

Scheme 4

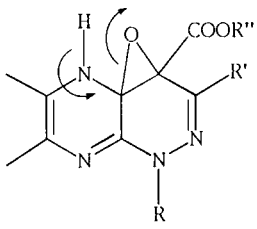


Decomposition of HNO_2

Chart 5

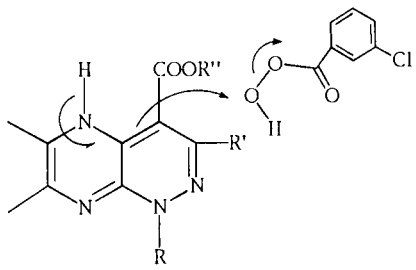


Postulated Oxidation Mechanism A



Postulated Oxidation Mechanism B

Chart 6



Postulated Oxidation Mechanism C

C_4=O carbon signals of compounds **6a** (δ 167.4 ppm) and **11a** (δ 171.9 ppm) were observed in slightly higher magnetic fields than the ester C=O carbon signals [**6a** (δ 173.5 ppm) and **11a** (δ 172.8 ppm)].

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.

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

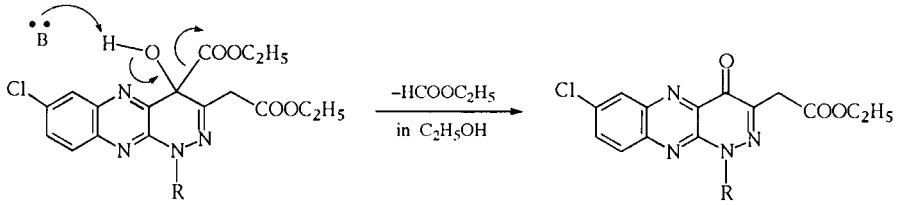
Method 1.

A solution of compound **1a** (10 g, 44.5 mmoles) and diethyl acetonedicarboxylate (13.49 g, 66.8 mmoles) in concentrated sulfuric acid (0.5 ml)/acetic acid (250 ml) was refluxed in an oil bath for 90 minutes. The solvent was evaporated *in vacuo* to give orange crystals of compound **5a**, which were triturated with ethanol and then collected by suction filtration (13.19 g, 76%). Recrystallization from *N,N*-dimethylformamide/ethanol gave orange needles.

Method 2.

A solution of compound **1a** (10 g, 44.5 mmoles) and diethyl acetonedicarboxylate (13.49 g, 66.8 mmoles) in acetic acid (250 ml) was refluxed in an oil bath for 90 minutes. The solvent was evaporated *in vacuo* to give orange crystals of compound **5a**, which were triturated with ethanol and collected by suction filtration (11.19 g, 64%). Recrystallization from *N,N*-dimethylformamide/ethanol gave orange needles.

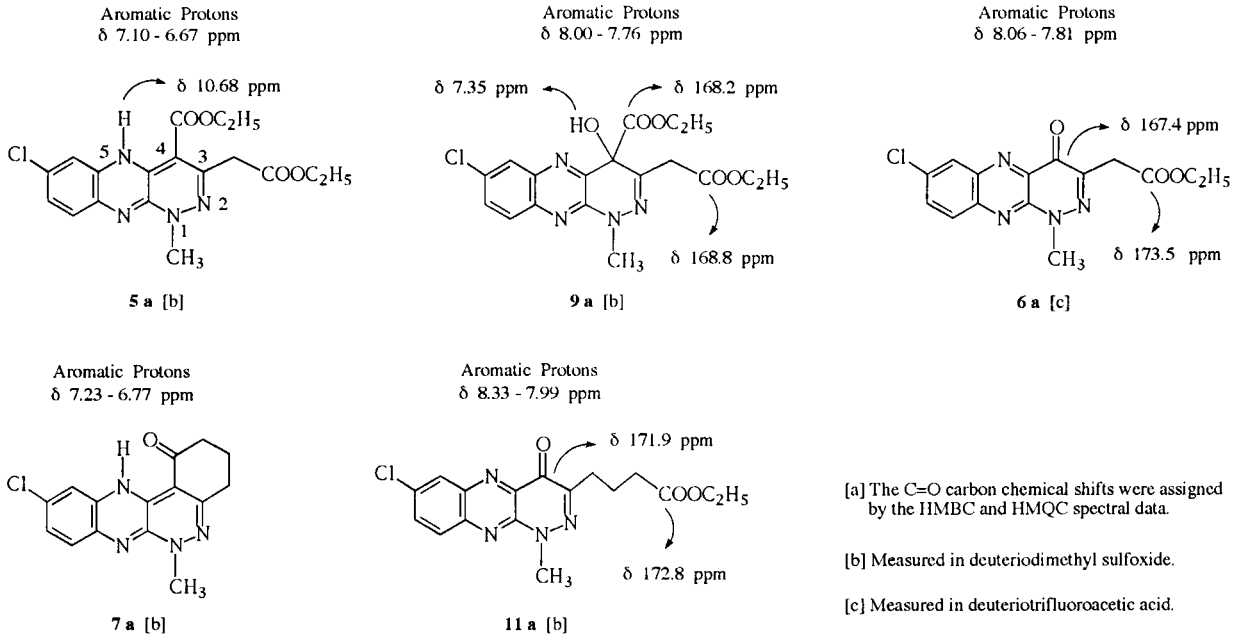
Scheme 5



9 a,b **6 a,b**

B : 1,8-Diazabicyclo[5.4.0]-7-undecene, Sodium Carbonate, or Hydrazine Hydrate

Chart 7 [a]



5 a [b] **9 a** [b] **6 a** [c]

7 a [b] **11 a** [b]

[a] The C=O carbon chemical shifts were assigned by the HMBC and HMQC spectral data.

[b] Measured in deuteriodimethyl sulfoxide.

[c] Measured in deuteriotrifluoroacetic acid.

Compound **5a** had mp 147-148°; ir: ν cm^{-1} 1742, 1738, 1655, 1605; ms: m/z 390 (M^+), 392 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 10.68 (s, 1H, N_5-H), 7.10 (d, J = 2.0 Hz, 1H, C_6-H), 6.78 (dd, J = 2.0, 8.5 Hz, 1H, C_8-H), 6.67 (d, J = 8.5 Hz, 1H, C_9-H), 4.17 (q, J = 7.0 Hz, 2H, ester CH_2), 4.05 (q, J = 7.0 Hz, 2H, ester CH_2), 3.37 (s, 2H, C_3-methylene CH_2) 3.13 (s, 3H, N_1-CH_3), 1.19 (t, J = 7.0 Hz, 3H, ester CH_3), 1.16 (t, J = 7.0 Hz, 3H, ester CH_3).

Anal. Calcd. for $C_{18}H_{19}ClN_4O_4$: C, 55.32; H, 4.90; Cl, 9.07; N, 14.34. Found: C, 55.24; H, 4.90; Cl, 9.11; N, 14.40.

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

A solution of compound **1b** (5 g, 21.0 mmoles) in concentrated sulfuric acid (0.3 ml)/acetic acid (125 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* gave brown crystals of compound **5b**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (6.82 g, 80%). Recrystallization from ethanol afforded brown needles, mp 131-132°; ir: ν cm^{-1} 1735, 1665, 1600; ms: m/z 404 (M^+), 406 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 10.71 (s, 1H, N_5-H), 7.10 (d, J = 2.0 Hz, 1H, C_6-H), 6.78 (dd, J = 2.0, 8.5 Hz, 1H, C_8-H), 6.66 (d, J = 8.5 Hz, 1H, C_9-H), 4.12 (q, J = 7.0 Hz, 2H, ester CH_2), 4.05 (q, J = 7.0 Hz, 2H, ester CH_2), 3.61 (q, J = 7.0 Hz, 2H, N_1-ethyl CH_2), 3.39 (s, 2H, C_3-methylene CH_2) 1.19 (t, J = 7.0 Hz, 3H, ester CH_3), 1.17 (t, J = 7.0 Hz, 3H, ester CH_3), 1.11 (t, J = 7.0 Hz, 3H, N_1-ethyl CH_3).

Anal. Calcd. for $C_{19}H_{21}ClN_4O_4$: C, 56.37; H, 5.23; Cl, 8.76; N, 13.84. Found: C, 56.15; H, 5.28; Cl, 9.06; N, 13.79.

10-Chloro-6-methyl-1-oxo-1,2,3,4,6,12-hexahydroquinoxalino-[2,3-*c*]cinnoline (**7a**).

Method 1.

A solution of compound **1a** (10 g, 44.5 mmoles) and 1,3-cyclohexanedione (7.48 g, 66.8 mmoles) in acetic acid (250 ml) was refluxed in an oil bath for 1 hour. Condensation of the solvent *in vacuo* to about half volume gave red crystals of compound **7a**, which were collected by suction filtration and washed with ethanol to afford an analytically pure sample (10.08 g). Evaporation of the filtrate *in vacuo* provided additional red crystals of compound **7a**, which were collected by suction filtration (2.72 g), total yield, 12.80 g (96%).

Method 2.

A solution of compound **1a** (1 g, 4.45 mmoles) and 1,3-cyclohexanedione (0.748 g, 6.68 mmoles) in *N,N*-dimethylformamide

(30 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* gave red crystals of compound **7a**, which were collected by suction filtration (0.41 g, 31%).

Compound **7a** had mp 253-254°; ir: ν cm^{-1} 1630, 1602, 1582; ms: m/z 300 (M^+), 302 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 12.01 (brs, 1H, N_{12}-H), 7.23 (d, J = 2.0 Hz, 1H, C_{11}-H), 6.85 (dd, J = 2.0, 8.5 Hz, 1H, C_9-H), 6.77 (d, J = 8.5 Hz, 1H, C_8-H), 3.15 (s, 3H, N_6-CH_3), 2.38 (t, J = 6.5 Hz, 2H, CH_2), 2.28 (t, J = 6.5 Hz, 2H, CH_2), 1.77 (tt, J = 6.5, 6.5 Hz, 2H, CH_2).

Anal. Calcd. for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; Cl, 11.79; N, 18.63. Found: C, 59.84; H, 4.34; Cl, 11.73; N, 18.56.

10-Chloro-6-ethyl-1-oxo-1,2,3,4,6,12-hexahydroquinoxalino[2,3-*c*]cinnoline (**7b**).

A solution of compound **1b** (5 g, 21.0 mmoles) and 1,3-cyclohexanedione (3.52 g, 31.4 mmoles) in acetic acid (250 ml) was refluxed in an oil bath for 1 hour. Evaporation of the solvent *in vacuo* gave red crystals of compound **7b**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (4.33 g, 66%). Recrystallization from acetic acid/water gave red needles, mp 200-201°; ir: ν cm^{-1} 2935, 1640, 1605, 1590, 1580; ms: m/z 314 (M^+), 316 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 12.00 (brs, 1H, N_{12}-H), 7.21 (d, J = 2.5 Hz, 1H, C_{11}-H), 6.85 (dd, J = 2.5, 8.5 Hz, 1H, C_9-H), 6.70 (d, J = 8.5 Hz, 1H, C_8-H), 3.62 (q, J = 7.0 Hz, 2H, N_6-ethyl CH_2), 2.38 (t, J = 6.5 Hz, 2H, CH_2), 2.29 (t, J = 6.5 Hz, 2H, CH_2), 1.77 (tt, J = 6.5, 6.5 Hz, 2H, CH_2), 1.11 (t, J = 7.0 Hz, 3H, N_6-ethyl CH_3).

Anal. Calcd. for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; Cl, 11.26; N, 17.80. Found: C, 60.82; H, 4.89; Cl, 11.33; N, 17.84.

Ethyl 7-Chloro-3-ethoxycarbonylmethylene-4-hydroxy-1-methyl-1,4-dihydropyridazino[3,4-*b*]quinoxaline-4-carboxylate (**9a**).

A solution of sodium nitrite (2.65 g, 38.4 mmoles) in water (50 ml) was added dropwise to a suspension of compound **5a** (10 g, 25.6 mmoles) in acetic acid (200 ml)/water (50 ml) with stirring in an ice-water bath. The reaction mixture was heated for 30 minutes on a boiling water bath, wherein aspiration was carried out through a T tube attached to the top of the condenser. After the reaction, water (200 ml) was added to the reaction mixture with heating on a boiling water bath. The reaction mixture was allowed to stand at room temperature to precipitate yellow prisms of compound **9a**, which were collected by suction filtration and washed with ethanol/water (1:1) to provide an analytically pure sample (8.34 g, 80%), mp 122-123°; ir: ν cm^{-1} 1742, 1738, 1600; ms: m/z 406 (M^+), 408 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 8.00 (d, J = 2.0 Hz, 1H, C_6-H), 7.88 (d, J = 9.0 Hz, 1H, C_9-H), 7.76 (dd, J = 2.0, 9.0 Hz, 1H, C_8-H), 7.35 (s, 1H, C_4-OH), 4.08 (q, J = 7.0 Hz, 4H, ester CH_2), 3.65 (s, 3H, N_1-CH_3), 3.48 (d, J = 16.0 Hz, 1H, C_3-methylene CH), 3.40 (d, J = 16.0 Hz, 1H, C_3-methylene CH), 1.18 (t, J = 7.0 Hz, 3H, ester CH_3), 1.03 (t, J = 7.0 Hz, 3H, ester CH_3).

Anal. Calcd. for $C_{18}H_{19}ClN_4O_5$: C, 53.14; H, 4.71; Cl, 8.71; N, 13.77. Found: C, 53.13; H, 4.77; Cl, 8.63; N, 13.76.

Ethyl 2-(7-Chloro-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]-quinoxalin-3-yl)acetate (**6a**).

Method 1.

A solution of compound **9a** (10 g, 24.6 mmoles) and 1,8-diazabicyclo[5.4.0]-7-undecene (1 ml) in ethanol (250 ml) was refluxed on a boiling water bath for 1 hour to precipitate brown crystals of compound **6a**, which were collected by suction filtration (7.75 g, 95%). Recrystallization from ethanol gave yellow prismic needles.

Method 2.

A solution of compound **9a** (1 g, 2.46 mmoles) and hydrazine hydrate (595 mg, 11.9 mmoles) in ethanol (50 ml) was refluxed on a boiling water bath for 2 hours to precipitate brown prismic needles of compound **6a**, which were collected by suction filtration (410 mg, 50%).

Compound **6a** had mp 207-208°; ir: ν cm^{-1} 1722, 1650; ms: m/z 332 (M^+), 334 ($M^+ + 2$); pmr (deuteriotrifluoroacetic acid): 8.06 (d, J = 2.0 Hz, 1H, C_6-H), 8.01 (d, J = 9.0 Hz, 1H, C_9-H), 7.81 (dd, J = 2.0, 9.0 Hz, 1H, C_8-H), 4.22 (s, 3H, N_1-CH_3), 3.98 (q, J = 7.0 Hz, 2H, ester CH_2), 3.85 (s, 2H, C_3-methylene CH_2), 0.96 (t, J = 7.0 Hz, 3H, ester 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, 54.07; H, 4.01; Cl, 10.66; N, 16.74.

Ethyl 2-(7-Chloro-1-ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]-quinoxalin-3-yl)acetate (**6b**).

A solution of compound **5b** (3 g, 7.42 mmoles) and *m*-chloroperbenzoic acid (70% purity, 2.74 g, 11.1 mmoles) in ethanol (100 ml) was refluxed on a boiling water bath for 1 hour. After the ethanol solution was cooled to room temperature, sodium carbonate (1.77 g, 16.7 mmoles) and water (50 ml) were added to this ethanol solution. The resulting mixture was refluxed on a boiling water bath for 1 hour and then filtered. The filtrate was evaporated *in vacuo* to a small volume, and 1 *N* hydrochloric acid (17 ml) was added to the solution to precipitate yellow crystals of compound **6b**, which were collected by suction filtration and then triturated with hot water (100 ml). Recrystallization from ethanol/water provided brown needles of compound **6b** (2.10 g, 82%), mp 170-171°; ir: ν cm^{-1} 1722, 1650; ms: m/z 346 (M^+), 348 ($M^+ + 2$); pmr (deuteriotrifluoroacetic acid): 8.40 (s, 1H, C_6-H), 8.15 (d, J = 9.0 Hz, 1H, C_9-H), 8.05 (d, J = 9.0 Hz, 1H, C_8-H), 4.65 (q, J = 7.0 Hz, 2H, N_1-ethyl CH_2), 4.11 (q, J = 7.0 Hz, 2H, ester CH_2), 3.79 (s, 2H, C_3-methylene CH_2), 1.44 (t, J = 7.0 Hz, 3H, N_1-ethyl CH_3), 1.18 (t, J = 7.0 Hz, 3H, ester CH_3).

Anal. Calcd. for $C_{16}H_{15}ClN_4O_3$: C, 55.42; H, 4.36; Cl, 10.22; N, 16.16. Found: C, 55.20; H, 4.42; Cl, 9.99; N, 15.87.

4-(7-Chloro-1-methyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]-quinoxalin-3-yl)butyric Acid (**8a**).

A solution of compound **7a** (10 g, 33.3 mmoles) and *N*-bromosuccinimide (13.05 g, 73.3 mmoles) in acetic acid (150 ml)/water (100 ml) was refluxed in an oil bath for 2 hours to precipitate orange crystals of compound **8a**, which were collected by suction filtration (8.13 g). Evaporation of the filtrate *in vacuo* gave additional orange crystals of compound **8a**, which were collected by suction filtration (0.63 g), total yield, 8.76 g (79%). Recrystallization from acetic acid/water provided orange prisms, mp 228-229°; ir: ν cm^{-1} 1710, 1639; ms: m/z 332 (M^+), 334 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 8.35 (dd, J = 2.0, 0.5 Hz, 1H, C_6-H), 8.10 (dd, J = 9.5, 0.5 Hz, 1H, C_9-H), 8.01 (dd, J = 9.5, 2,0 Hz, 1H, C_8-H), 4.09 (s, 3H, N_1-CH_3), 2.75 (t, J = 7.0 Hz, 2H, CH_2), 2.33 (t, J = 7.0 Hz, 2H, CH_2), 1.89 (tt, J = 7.0, 7.0 Hz, 2H, CH_2). The COOH proton signal was not observed because of the presence of moisture in a solution.

Anal. Calcd. for $C_{15}H_{13}ClN_4O_3$: C, 54.14; H, 3.94; Cl, 10.65; N, 16.84. Found: C, 53.89; H, 4.06; Cl, 10.55; N, 16.70.

4-(7-Chloro-1-ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)butyric Acid (**8b**).

A suspension of compound **7b** (2.5 g, 7.95 mmoles) and *N*-bromosuccinimide (3.54 g, 19.9 mmoles) in acetic acid (50

ml)/water (30 ml) was refluxed in an oil bath for 2 hours to give a clear solution. The solution was allowed to stand overnight to precipitate orange needles of compound **8b**, which were collected by suction filtration (2.47 g, 90%). Recrystallization from ethanol provided orange needles, mp 152-153°; ir: ν cm^{-1} 1710, 1639; ms: m/z 346 (M^+), 348 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 8.35 (d, J = 2.0 Hz, 1H, C_6-H), 8.10 (d, J = 9.0 Hz, 1H, C_9-H), 8.00 (dd, J = 9.0, 2.0 Hz, 1H, C_8-H), 4.60 (q, J = 7.0 Hz, 2H, N_1-ethyl CH_2), 2.76 (t, J = 7.0 Hz, 2H, CH_2), 2.32 (t, J = 7.0 Hz, 2H, CH_2), 1.90 (tt, J = 7.0, 7.0 Hz, 2H, CH_2), 1.42 (t, J = 7.0 Hz, 3H, N_1-ethyl CH_3). The COOH proton signal was not observed because of the presence of moisture in a solution.

Anal. Calcd. for $C_{16}H_{15}ClN_4O_3$: C, 55.42; H, 4.36; Cl, 10.22; N, 16.16. Found: C, 55.45; H, 4.33; Cl, 10.06; N, 15.94.

Ethyl 4-(7-Chloro-1-methyl-4-oxo-1,4-dihydropyridazino-[3,4-*b*]quinoxalin-3-yl)butyrate (**11a**).

A suspension of compound **8a** (2 g) in concentrated sulfuric acid (0.5 ml)/ethanol (100 ml) was refluxed in an oil bath for 2 hours to give a clear solution. The solution was allowed to stand overnight at room temperature to precipitate reddish brown needles of compound **11a**, which were collected by suction filtration and washed with ethanol and then *n*-hexane to afford an analytically pure sample (1.73 g, 80%), mp 120-121°; ir: ν cm^{-1} 1730, 1635, 1600; ms: m/z 360 (M^+), 362 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 8.33 (dd, J = 2.0, 0.5 Hz, 1H, C_6-H), 8.08 (dd, J = 9.0, 0.5 Hz, 1H, C_9-H), 7.99 (dd, J = 9.0, 2,0 Hz, 1H, C_8-H), 4.07 (s, 3H, N_1-CH_3), 4.02 (q, J = 7.0 Hz, 2H, ester CH_2), 2.74 (t, J = 7.5 Hz, 2H, CH_2), 2.40 (t, J = 7.5 Hz, 2H, CH_2), 1.91 (tt, J = 7.5, 7.5 Hz, 2H, CH_2), 1.15 (t, J = 7.0 Hz, 3H, ester CH_3).

Anal. Calcd. for $C_{17}H_{17}ClN_4O_3$: C, 56.59; H, 4.75; Cl, 9.83; N, 15.53. Found: C, 56.33; H, 4.75; Cl, 9.68; N, 15.47.

Ethyl 4-(7-Chloro-1-ethyl-4-oxo-1,4-dihydropyridazino[3,4-*b*]-quinoxalin-3-yl)butyrate (**11b**).

A suspension of compound **8b** (1.5 g) in concentrated sulfuric acid (0.5 ml)/ethanol (60 ml) was refluxed in an oil bath for 2 hours to give a clear solution. The solution was allowed to stand overnight to precipitate orange needles of compound **11b**, which were collected by suction filtration and washed with *n*-hexane to afford an analytically pure sample (1.15 g, 71%), mp 185-186°; ir: ν cm^{-1} 1740, 1639; ms: m/z 374 (M^+), 376 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 8.36 (d, J = 2.0 Hz, 1H, C_6-H), 8.11 (d, J = 9.0 Hz, 1H, C_9-H), 8.01 (dd, J = 9.0, 2,0 Hz, 1H, C_8-H), 4.61 (q, J = 7.0 Hz, 2H, N_1-ethyl CH_2), 4.01(q, J = 7.0 Hz, 2H, ester CH_2), 2.77 (t, J = 7.0 Hz, 2H, CH_2), 2.40 (t, J = 7.0 Hz, 2H, CH_2), 1.93 (tt, J = 7.0, 7.0 Hz, 2H, CH_2), 1.42 (t, J = 7.0 Hz, 3H, N_1-ethyl CH_3), 1.14 (t, J = 7.0 Hz, 3H, ester CH_3).

Anal. Calcd. for $C_{18}H_{19}ClN_4O_3$: C, 57.68; H, 5.11; Cl, 9.46; N, 14.95. Found: C, 57.61; H, 5.07; Cl, 9.58; N, 15.03.

4-(7-Chloro-4-hydroxyimino-1-methyl-1,4-dihydropyridazino-[3,4-*b*]quinoxalin-3-yl)butyric Acid (**12**).

A solution of compound **8a** (10 g, 30.1 mmoles) and hydroxylamine hydrochloride (5.22 g, 75.3 mmoles) in pyridine (200 ml) was refluxed in an oil bath for 5 hours. The reaction mixture was cooled to room temperature and then filtered. Evaporation of the filtrate *in vacuo* gave red crystals of compound **12**, which were collected by suction filtration (6.74 g, 64%). Recrystallization from dioxane provided red prismic needles, mp 226-227°; ir: ν cm^{-1} 3450, 1700, 1638, 1602; ms: m/z 347 (M^+), 349 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 14.84 (s, 1H, OH), 12.00 (br, 1H, OH), 8.09 (dd, J = 2.0, 0.5 Hz, 1H, C_6-H), 7.75 (dd, J = 9.0, 2.0 Hz, 1H, C_8-H), 7.70 (dd, J = 9.0, 0.5 Hz, 1H, C_9-H), 3.65 (s, 3H, N_1-CH_3), 2.57 (t, J = 7.0 Hz, 2H, CH_2), 2.30 (t, J = 7.0 Hz, 2H, CH_2), 1.86 (tt, J = 7.0, 7.0 Hz, 2H, CH_2).

Anal. Calcd. for $C_{15}H_{14}ClN_5O_3$: C, 51.81; H, 4.06; Cl, 10.19; N, 20.14. Found: C, 52.04; H, 4.14; Cl, 10.18; N, 19.97.

Ethyl 4-(7-Chloro-4-hydroxyimino-1-methyl-1,4-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)butyrate (**13**).

A suspension of compound **12** (5 g) in concentrated sulfuric acid (1 ml)/ethanol (250 ml) was refluxed in an oil bath for 2 hours to give a clear solution. The solution was allowed to stand overnight at room temperature to precipitate red needles of compound **13**, which were collected by suction filtration and washed with ethanol and then *n*-hexane to provide an analytically pure sample (4.73 g, 88%), mp 150-151°; ir: ν cm^{-1} 3440, 1730; ms: m/z 375 (M^+), 377 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 14.81 (brs, 1H, OH), 8.09 (d, J = 2.0 Hz, 1H, C_6-H), 7.75 (dd, J = 9.0, 2,0 Hz, 1H, C_8-H), 7.70 (d, J = 9.0 Hz, 1H, C_9-H), 4.02 (q, J = 7.0 Hz, 2H, ester CH_2), 3.65 (s, 3H, N_1-CH_3), 2.57 (t, J = 7.0 Hz, 2H, CH_2), 2.38 (t, J = 7.0 Hz, 2H, CH_2), 1.88 (tt, J = 7.0, 7.0 Hz, 2H, CH_2), 1.15 (t, J = 7.0 Hz, 3H, ester CH_3).

Anal. Calcd. for $C_{17}H_{18}ClN_5O_3$: C, 54.33; H, 4.83; Cl, 9.43; N, 18.64. Found: C, 54.06; H, 4.80; Cl, 9.36; N, 18.41.

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