# Synthesis of Pyrrolo[1,2-*a*]quinoxalines by 1,3-Dipolar Cycloaddition Reaction. An Additional Reaction Mechanism *via* An Aziridine Intermediate.

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The reaction of the 2-substituted 6-chloroquinoxaline 4-oxides **1a** or **1b** with 2-fold molar amount of methyl propiolate resulted in the 1,3-dipolar cycloaddition reaction to give 8-chloro-1,3-bismethoxycarbonyl-4-(piperidin-1-yl)pyrrolo[1,2-*a*]quinoxaline **4a** or 8-chloro-1,3-bismethoxycarbonyl-4-(morpholin-4-yl)pyrrolo-[1,2-*a*]quinoxaline **4b**, respectively. Compound **4a** or **4b** was transformed into 8-chloro-3-methoxycarbonyl-4-(piperidin-1-yl)pyrrolo[1,2-*a*]quinoxaline **5a** or 8-chloro-3-methoxycarbonyl-4-(morpholin-4-yl)pyrrolo[1,2-*a*]-quinoxaline **5b**, respectively. The structure of **4a,b** was confirmed by the NOE measurement among the $C_1$-H, $C_2$-H and $C_9$-H proton signals of **5a,b**. An additional reaction mechanism was proposed for the ring transformation of isoxazolo[2,3-*a*]quinoxalines into pyrrolo[1,2-*a*]quinoxalines.

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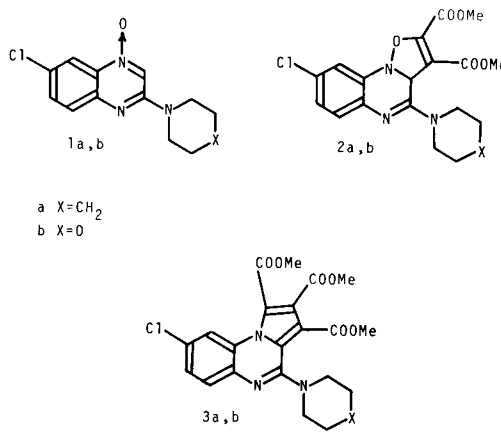
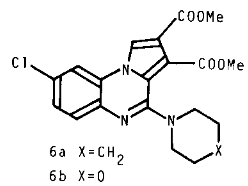
In a previous paper [2], we reported a selective synthesis of the isoxazolo[2,3-*a*]quinoxalines **2a,b** and pyrrolo[1,2-*a*]-quinoxalines **3a,b** from the 2-substituted 6-chloroquinoxalines **1a,b** (Chart 1). Moreover, the pyrrolo[1,2-*a*]quinoxalines **3a,b** were clarified to be produced by the ring trans-

Chart 1



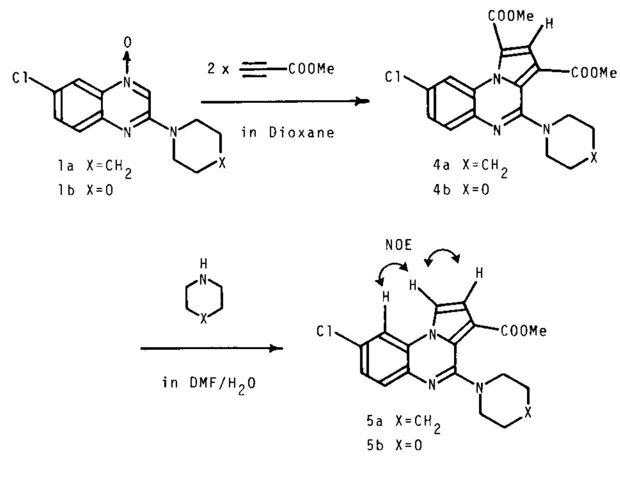

formation of the isoxazolo[2,3-*a*]quinoxalines **2a,b**. Concerning the ring transformation, we presented the reaction mechanism *via* the isoxazoline ring opening [3] (Scheme 2-I), but we could not obtain any evidence to determine the reaction mechanism *via* an aziridine intermediate **A** (Scheme 2-II) which would be formed by the thermal isomerization of the isoxazoline ring [4-7]. In the present investigation, however, we found that the pyrrolo[1,2-*a*]quinoxalines **4a,b** were synthesized by the 1,3-dipolar cyclo-

Chart 2

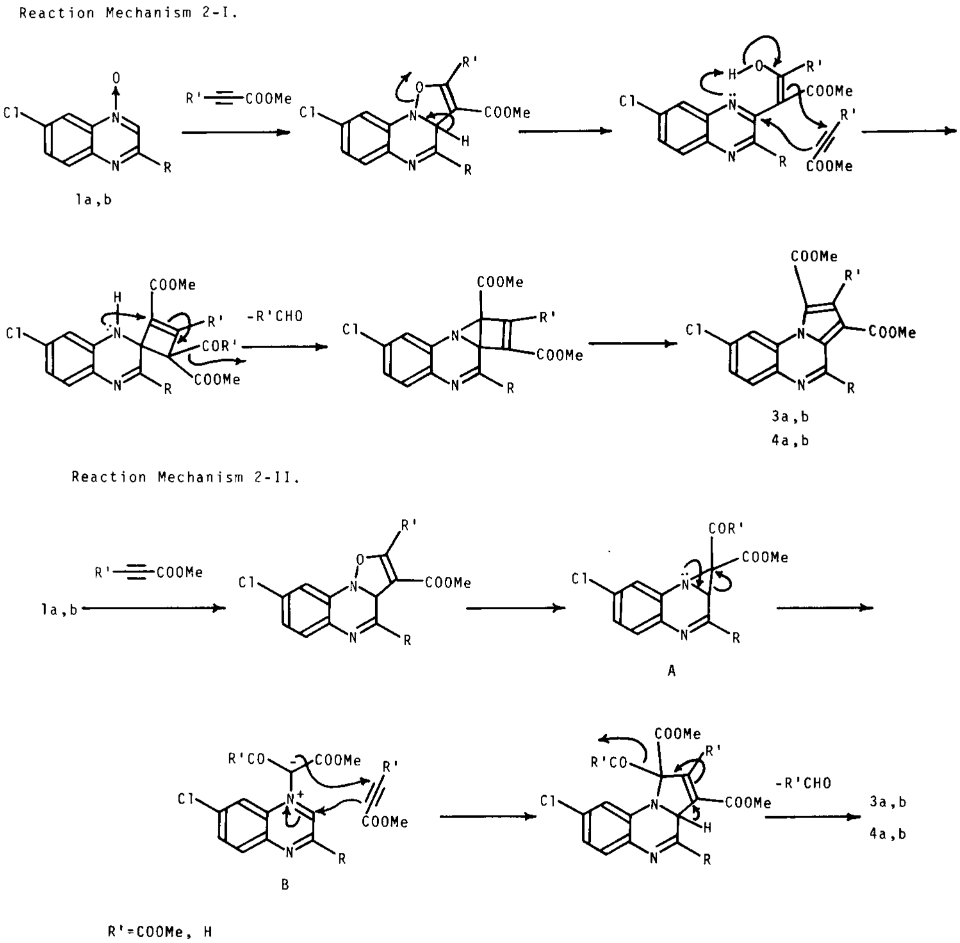



addition reaction of **1a,b** (Scheme 1). The synthesis and structural establishment of **4a,b** enabled us to propose the mechanism *via* an aziridine intermediate **A** (Scheme 2-II). Furthermore, we could assign three ester methyl proton signals of the pyrrolo[1,2-*a*]quinoxalines **3a,b** in comparison with the methyl proton signals of the pyrrolo[1,2-*a*]quinoxalines **4a,b**, **5a,b** and **6a,b** [8] (Chart 2). This paper describes the synthesis of **4a,b** and **5a,b** (Scheme 1), a new

Scheme 1



Scheme 2




reaction mechanism for the ring transformation of the isoxazolo[2,3-*a*]quinoxalines into the pyrrolo[1,2-*a*]quinoxalines (Scheme 2) and the assignment of the ester methyl proton signals (Table 2).

The reaction of **1a** or **1b** with 2-fold molar amount of methyl propiolate gave 8-chloro-1,3-bismethoxycarbonyl-4-(piperidin-1-yl)pyrrolo[1,2-*a*]quinoxaline **4a** or 8-chloro-1,3-bismethoxycarbonyl-4-(morpholin-4-yl)pyrrolo[1,2-*a*]quinoxaline **4b**, respectively. Refluxing of **4a** or **4b** and piperidine or morpholine in *N,N*-dimethylformamide/water resulted in the elimination of the $C_1$-ester group [2] to afford 8-chloro-3-methoxycarbonyl-4-(piperidin-1-yl)pyrrolo[1,2-*a*]quinoxaline **5a** or 8-chloro-3-methoxycarbonyl-4-(morpholin-4-yl)pyrrolo[1,2-*a*]quinoxaline **5b**, respectively.

The structure of **4a,b** and **5a,b** was established by the spectral and analytical data. The $C_2$-H proton signal of **4a**

Table 1

NOE Data for Compounds **5a,b**

| Compound | Radiation | NOE % $C_1$-H | $C_2$-H | $C_9$-H |
|---|---|---|---|---|
| **5a** | $C_1$-H | | 8.3 | 14.6 |
| | $C_2$-H | 4.9 | | |
| | $C_9$-H | 15.7 | | |
| **5b** | $C_1$-H | | 11.6 | 14.2 |
| | $C_2$-H | 4.9 | | |
| | $C_9$-H | 14.7 | | |

Table 2

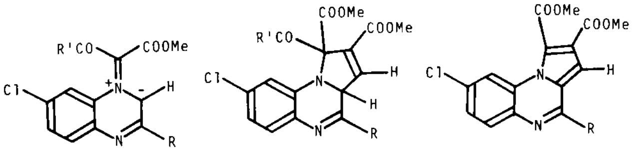
Assignment of Ester Methyl Proton Signals for Compounds **3a,b**-**6a,b**

| Compound | Chemical Shift (δ) $C_1$-$COOCH_3$ | $C_2$-$COOCH_3$ | $C_3$-$COOCH_3$ |
|---|---|---|---|
| **3a** | 4.02 | 3.88 | 3.85 |
| **3b** | 4.04 | 3.89 | 3.86 |
| **4a** | 3.94 | | 3.86 |
| **4b** | 3.94 | | 3.86 |
| **5a** | | | 3.83 |
| **5b** | | | 3.83 |
| **6a** | | 3.88 | 3.84 |
| **6b** | | 3.88 | 3.84 |

and **4b** was observed at $\delta$ 7.75 and 7.78 ppm, respectively, while the $C_1$-H proton signal of **6a** and **6b** [8] (Chart 2) appeared at $\delta$ 9.02 and 9.08 ppm, respectively. Moreover, the NOE was observed among the $C_1$-H, $C_2$-H and $C_9$-H proton signals of **5a,b** (Table 1). These data ascertained the structure of **4a,b** and **5a,b**.

The reaction mechanism including the formation of **3a,b** [2] and **4a,b** from **1a,b** is shown in Scheme 2-I and 2-II. The isoxazoline ring opening mechanism 2-I exhibited no discrepancy for the production of both **3a,b** and **4a,b**. In the mechanism 2-II, the aziridine ring opening was found to give an intermediate **B**, but not **C** (Chart 3), because the 1,3-dipolar cycloaddition reaction of **C** with methyl propiolate would afford the pyrrolo[1,2-*a*]quinoxaline **E** *via* an intermediate **D** (Chart 3).

Chart 3




C D E

From the nmr spectral data for **3a,b-6a,b**, the ester methyl proton signals were assigned as shown in Table 2. The $C_1$-, $C_2$- and $C_3$-ester methyl proton signals were observed at $\delta$ 4.40-3.94, 3.89-3.88 and 3.86-3.83 ppm, respectively.

## 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 IRA-1 spectrophotometer. The nmr spectra were measured in deuteriodimethyl sulfoxide with a VXR-300 spectrometer at 300 MHz. Chemical shifts are given in the $\delta$ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

8-Chloro-1,3-bismethoxycarbonyl-4-(piperidin-1-yl)pyrrolo[1,2-*a*]quinoxaline **4a**.

A solution of **1a** (5 g, 19.0 mmoles) and methyl propiolate (3.99 g, 47.5 mmoles) in dioxane (150 ml) was refluxed in an oil bath for 10 hours. Evaporation of the solvent *in vacuo* left an oily residue, which was dissolved in hot ethanol. Cooling of the solution to room temperature precipitated analytically pure yellow needles **4a**, which were collected by suction filtration (1.20 g, 16%), mp 160-161°; ir: $\nu$ cm$^{-1}$ 3120, 2940, 2850, 1710; ms: m/z 401 (M$^+$), 403 (M$^+$+2); pmr: 8.45 (d, J = 2.2 Hz, 1H, $C_9$-H), 7.75 (s, 1H, $C_2$-H), 7.64 (d, J = 8.5 Hz, 1H, $C_6$-H), 7.49 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H, $C_7$-H), 3.94 (s, 3H, $C_1$-$COOCH_3$), 3.86 (s, 3H, $C_3$-$COOCH_3$), 3.39 (s, 4H, $CH_2$-N-$CH_2$), 1.60 (s, 6H, $CH_2$-$CH_2$-$CH_2$).

*Anal.* Calcd. for $C_{20}H_{20}ClN_3O_4$: C, 59.78; H, 5.02; Cl, 8.82; N, 10.46. Found: C, 59.56; H, 4.96; Cl, 8.86; N, 10.40.

8-Chloro-1,3-bismethoxycarbonyl-4-(morpholin-4-yl)pyrrolo[1,2-*a*]quinoxaline **4b**.

A solution of **1b** (5 g, 18.8 mmoles) and methyl propiolate (3.95 g, 47.0 mmoles) in dioxane (150 ml) was refluxed in an oil bath for 10 hours. Evaporation of the solvent *in vacuo* left an oily residue, which was dissolved in hot ethanol. Cooling of the solution to room temperature precipitated yellow needles **4b**, which were collected by suction filtration (2.12 g, 28%), mp 178-179°; ir: $\nu$ cm$^{-1}$ 3140, 2960, 2910, 2860, 1730, 1725; ms: m/z 403 (M$^+$), 405 (M$^+$+2); pmr: 8.45 (d, J = 2.1 Hz, 1H, $C_9$-H), 7.78 (s, 1H, $C_2$-H), 7.67 (d, J = 8.5 Hz, 1H, $C_6$-H), 7.51 (dd, J = 2.1 Hz, J = 8.5 Hz, 1H, $C_7$-H), 3.94 (s, 3H, $C_1$-$COOCH_3$), 3.86 (s, 3H, $C_3$-$COOCH_3$), 3.71 (t, J = 4.5 Hz, 4H, $CH_2$-O-$CH_2$), 3.39 (t, J = 4.5 Hz, 4H, $CH_2$-N-$CH_2$).

*Anal.* Calcd. for $C_{19}H_{18}ClN_3O_5$: C, 56.51; H, 4.49; Cl, 8.78; N, 10.41. Found: C, 56.36; H, 4.49; Cl, 8.86; N, 10.39.

8-Chloro-3-methoxycarbonyl-4-(piperidin-1-yl)pyrrolo[1,2-*a*]quinoxaline **5a**.

A solution of **4a** (600 mg) and piperidine (0.5 ml) in *N,N*-dimethylformamide (30 ml)/water (0.5 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* left an oily substance, which was crystallized from ethanol/water to provide analytically pure yellow prisms **5a**. The yellow prisms **5a** were collected by suction filtration (270 mg, 53%), mp 148-149°; ir: $\nu$ cm$^{-1}$ 1705; ms: m/z 343 (M$^+$), 345 (M$^+$+2); pmr: 8.43 (d, J = 3.0 Hz, 1H, $C_1$-H), 8.38 (d, J = 2.0 Hz, 1H, $C_9$-H), 7.58 (d, J = 8.5 Hz, 1H, $C_6$-H), 7.41 (dd, J = 2.0 Hz, J = 8.5 Hz, 1H, $C_7$-H), 7.13 (d, J = 3.0 Hz, 1H, $C_2$-H), 3.83 (s, 3H, $CH_3$), 3.40 (s, 4H, $CH_2$-N-$CH_2$), 1.60 (s, 6H, $CH_2$-$CH_2$-$CH_2$).

*Anal.* Calcd. for $C_{18}H_{18}ClN_3O_2$: C, 62.88; H, 5.28; Cl, 10.31; N, 12.22. Found: C, 62.60; H, 5.25; Cl, 10.14; N, 12.22.

8-Chloro-3-methoxycarbonyl-4-(morpholin-4-yl)pyrrolo[1,2-*a*]quinoxaline **5b**.

A solution of **4b** (1 g) and morpholine (0.5 ml) in *N,N*-dimethylformamide (30 ml)/water (0.5 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* left an oily substance, which was crystallized from ethanol/water to give analytically pure yellow needles **5b**. The yellow needles **5b** were collected by suction filtration (460 mg, 54%), mp 198-199°; ir: $\nu$ cm$^{-1}$ 1710; ms: m/z 345 (M$^+$), 347 (M$^+$+2); pmr: 8.48 (d, J = 3.0 Hz, 1H, $C_1$-H), 8.42 (d, J = 2.1 Hz, 1H, $C_9$-H), 7.63 (d, J = 8.5 Hz, 1H, $C_6$-H), 7.45 (dd, J = 2.1 Hz, J = 8.5 Hz, 1H, $C_7$-H), 7.19 (d, J = 3.0 Hz, 1H, $C_2$-H), 3.83 (s, 3H, $CH_3$), 3.73 (t, J = 4.5 Hz, 4H, $CH_2$-O-$CH_2$), 3.37 (t, J = 4.5 Hz, 4H, $CH_2$-N-$CH_2$).

*Anal.* Calcd. for $C_{17}H_{16}ClN_3O_3$: C, 59.05: H, 4.66; Cl, 10.25; N, 12.15. Found: C, 58.85; H, 4.65; Cl, 10.13; N, 11.90.

## REFERENCES AND NOTES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