A Selective Synthesis of Novel Isoxazolo[2,3-*a*]-quinoxalines and Pyrrolo[1,2-*a*]quinoxalines

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The isoxazolo[2,3-*a*]quinoxalines **11a,b** and pyrrolo[1,2-*a*]quinoxalines **12a,b** were selectively synthesized from the 2-substituted 6-chloroquinoxaline 4-oxides **10a,b**. The pyrrolo[1,2-*a*]quinoxalines **12a,b** were clarified to be produced by the ring transformation of the isoxazolo[2,3-*a*]quinoxalines **11a,b**.

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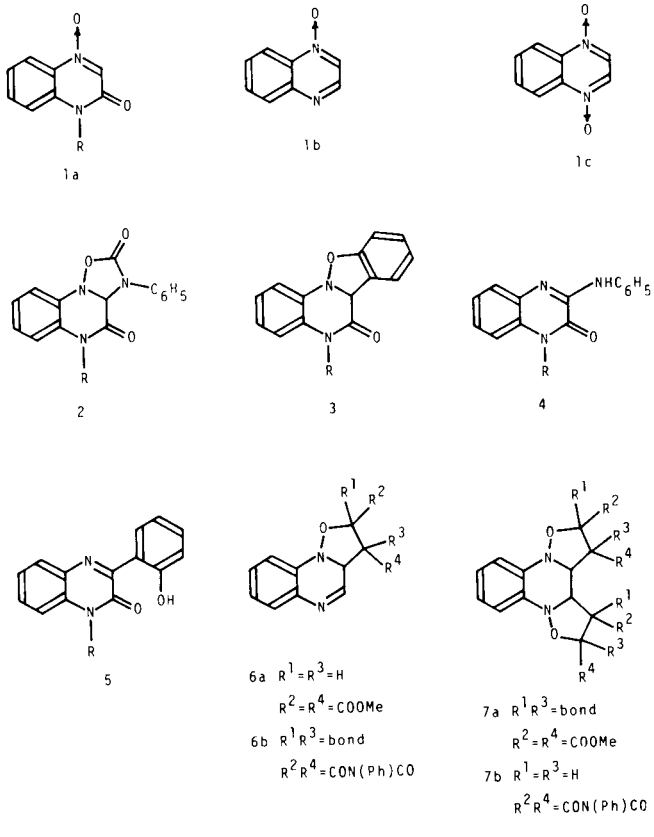
There have been a few papers concerning the 1,3-dipolar cycloaddition reaction of quinoxaline 4-oxide **1a**, 1-oxide **1b** or 1,4-dioxide **1c** with some dipolarophiles. For example, the reaction of **1a** with phenyl isocyanate or benzyne gave an intermediate **2** or **3**, whose ring opening formed the products **4** or **5**, respectively [2]. On the other hand, the reaction of **1b** with dimethyl malonate or *N*-phenylmaleimide afforded the isoxazolo[2,3-*a*]quinoxaline **6a** or **6b**, respectively [3], and the reaction of **1c** with dimethyl acetylenedicarboxylate (DMAD) or *N*-phenylmaleimide provided the diisoxazolo[2,3-*a*:3′,2′-*c*]quinoxaline **7a** or **7b**, respectively [3] (Chart 1). However, there has been no paper concerning the synthesis of pyrrolo[1,2-*a*]quinoxalines by the 1,3-dipolar cycloaddition reaction of quinoxaline *N*-oxides or by the ring transformation of isoxazolo[2,3-*a*]quinoxalines [4]. In the present investigation, we found that the 2-substituted 6-chloroquinoxaline 4-oxides **10** were selectively transformed into the isoxazolo[2,3-*a*]quinoxalines **11** and pyrrolo[1,2-*a*]quinoxalines **12** (Scheme 1). Moreover, the pyrrolo[1,2-*a*]quinoxalines **12** were found to be produced by the ring transformation of the isoxazolo[2,3-*a*]quinoxalines **11**. This paper describes the above selective synthesis of **11** and **12** together with a postulated mechanism for the ring transformation of **11** into **12**.

Chart 1



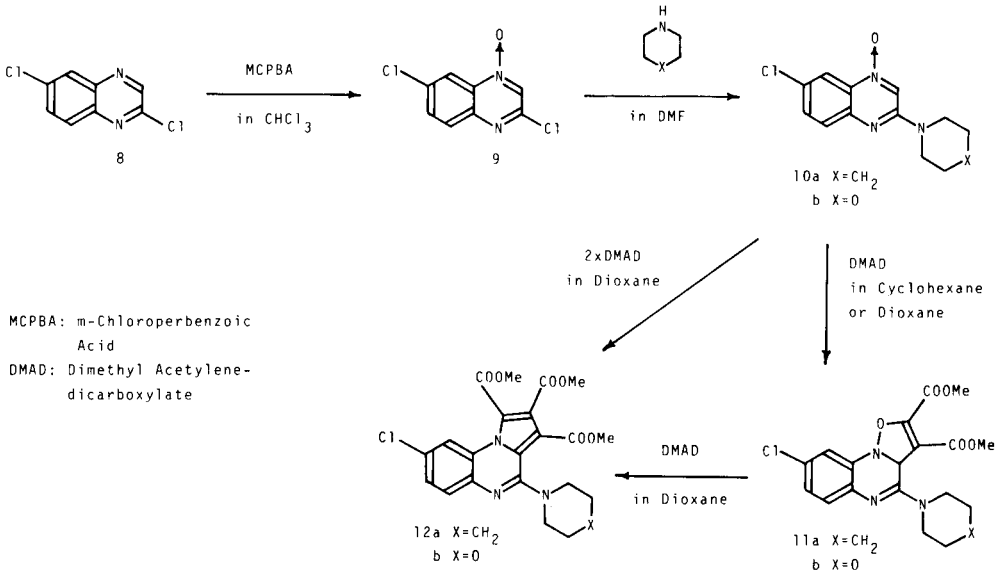
The reaction of 2,6-dichloroquinoxaline **8** [5] with *m*-chloroperbenzoic acid gave 2,6-dichloroquinoxaline 4-oxide **9**, whose reaction with piperidine or morpholine afforded 6-chloro-2-(piperidin-1-yl)quinoxaline 4-oxide **10a** or 6-chloro-2-(morpholin-4-yl)quinoxaline 4-oxide **10b**, respectively. The reaction of **10a** or **10b** with an equimolar amount of DMAD provided 8-chloro-2,3-bismethoxycarbonyl-4-(piperidin-1-yl)-3a*H*-isoxazolo[2,3-*a*]quinoxaline **11a** or 8-chloro-2,3-bismethoxycarbonyl-4-(morpholin-4-yl)-3a*H*-isoxazolo[2,3-*a*]quinoxaline **11b**, respectively. On the other hand, the reaction of **10a** or **10b** with 2-fold molar amount of DMAD furnished 8-chloro-1,2,3-trismethoxycarbonyl-4-(piperidin-1-yl)pyrrolo[1,2-*a*]quinoxaline **12a** or 8-chloro-1,2,3-trismethoxycarbonyl-4-(morpholin-4-yl)-pyrrolo[1,2-*a*]quinoxaline **12b**, respectively. The reaction of **11a** or **11b** with an equimolar amount of DMAD resulted in ring transformation to give **12a** or **12b**, respectively. A postulated reaction mechanism of the above sequential reactions is shown in Scheme 2.

The structural assignment for the above new compounds **9-12** was based on the analytical and spectral data. The composition of the isoxazolo[2,3-*a*]quinoxalines **11a,b** was checked by the high resolution mass spectral data, since **11a,b** were rather unstable for heating and decomposed while recrystallization.

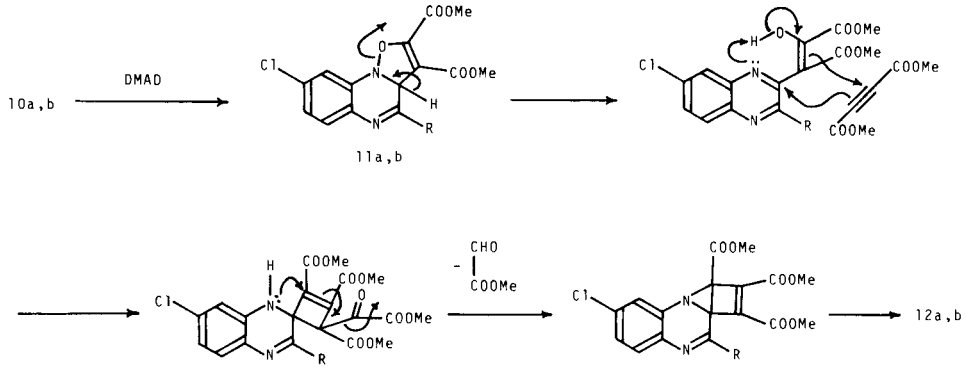
EXPERIMENTAL

All melting points were determined on a Ishii melting point apparatus and are uncorrected. The ir spectra (potassium bromide)

Scheme 1



Scheme 2



were recorded with a JASCO IRA-1 spectrophotometer. The nmr spectra were measured in deuteriodimethylsulfoxide with a VXR-300 spectrometer at 300 MHz. 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.

2,6-Dichloroquinoxaline 4-Oxide **9**.

A solution of **8** (20 g, 0.10 mole) and *m*-chloroperbenzoic acid (27.2 g, 1.1 equivalents) in chloroform (500 ml) was heated at 60° on a water bath for 7 hours. Removal of the solvent *in vacuo* gave crystals, which were triturated with saturated sodium bicarbonate solution to exclude *m*-chlorobenzoic acid and residual *m*-chloroperbenzoic acid. The crystals were collected by suction filtration and recrystallized from *N,N*-dimethylformamide/ethanol provided pale yellow needles **9** (15.5 g, 72%); mp 176-178°; ir: ν cm^{-1} 3060, 1595, 1228; ms: m/z 215 (M^+), 217 ($M^+ + 2$); pmr: 8.94 (s, 1H, C_3-H), 8.35 (d, J = 2.5 Hz, 1H, C_5-H), 8.07 (d, J = 9.0 Hz, 1H, C_8-H), 7.83 (dd, J = 2.5 Hz, J = 9.0 Hz, 1H, C_7-H).

Anal. Calcd. for $C_8H_4Cl_2N_2O$: C, 44.68; H, 1.87; Cl, 32.98; N, 13.03. Found: C, 44.80; H, 1.89; Cl, 32.95; N, 12.84.

6-Chloro-2-(piperidin-1-yl)quinoxaline 4-Oxide **10a** and 6-Chloro-2-(morpholin-4-yl)quinoxaline 4-Oxide **10b**.

A solution of **9** (10 g, 46.5 mmoles) and piperidine (5.94 g, 69.75 mmoles) or morpholine (6.08 g, 69.75 mmoles) in *N,N*-dimethylformamide (300 ml) was refluxed in an oil bath for 3 hours. Removal of the solvent *in vacuo* gave yellow crystals **10a** or **10b**, which were collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles **10a** (7.24 g, 59%) or **10b** (8.53 g, 69%).

Compound **10a**.

This compound had mp 165-166°; ir: ν cm^{-1} 3070, 2910, 1572, 1215; ms: m/z 263 (M^+), 265 ($M^+ + 2$); pmr: 8.59 (s, 1H, C_3-H), 8.14 (d, J = 2.0 Hz, 1H, C_5-H), 7.66-7.55 (m, 2H, C_7-H and C_8-H), 3.68 (t, J = 4.5 Hz, 4H, CH_2-N-CH_2), 1.69-1.51 (m, 6H, CH_2-CH_2-CH_2).

Anal. Calcd. for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; Cl, 13.44; N, 15.93. Found: C, 59.30; H, 5.48; Cl, 13.23; N, 15.65.

Compound **10b**.

This compound had mp 152-153°; ir: ν cm^{-1} 3070, 2940, 1570, 1220; ms: m/z 265 (M^+), 277 ($M^+ + 2$); pmr: 8.64 (s, 1H, C_3-H), 8.17

(d, J = 2.0 Hz, 1H, C_5-H), 7.71-7.58 (m, 2H, C_7-H and C_8-H), 3.75-3.62 (m, 8H, morpholine CH_2).

Anal. Calcd. for $C_{12}H_{12}ClN_3O_2$: C, 54.25; H, 4.55; Cl, 13.34; N, 15.82. Found: C, 54.24; H, 4.52; Cl, 13.49; N, 15.65.

8-Chloro-2,3-bismethoxycarbonyl-4-(piperidin-1-yl)-3a*H*-isoxazolo-[2,3-*a*]quinoxaline **11a**.

A suspension of **10a** (2 g, 7.6 mmoles) and dimethyl acetylenedicarboxylate (1.2 g, 8.36 mmoles) in cyclohexane (200 ml) was refluxed on a boiling water bath for 1 hour to precipitate red needles **11a**, which were collected by suction filtration and then triturated with ethanol (drying: below 80° *in vacuo*) (3.02 g, 98%), mp 224-225°; ir: ν cm^{-1} 3050, 2920, 1730, 1655, 1595; ms: m/z 405 (M^+), 407 (M^+ +2); pmr: 9.35 (s, 1H), 7.90 (s, 2H), 7.70 (s, 1H) (C_{3a}-H, C_6-H, C_7-H and C_9-H), 3.85 (s, 4H, CH_2-N-CH_2), 3.79 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 1.65 (s, 6H, CH_2-CH_2-CH_2).

Calcd. for $C_{19}H_{20}ClN_3O_5$: 405.109 (M^+), 407.106 (M^+ + 2). Found: 405.110 (M^+), 407.105 (M^+ +2).

8-Chloro-2,3-bismethoxycarbonyl-4-(morpholin-4-yl)-3a*H*-isoxazolo[2,3-*a*]quinoxaline **11b**.

A suspension of **10b** (2 g, 7.6 mmoles) and dimethyl acetylenedicarboxylate (1.19 g, 8.36 mmoles) in dioxane (60 ml) was refluxed in an oil bath for 1 hour to precipitate red needles **11b**, which were collected by suction filtration and then triturated with ethanol (drying: below 50° *in vacuo*) (2.97 g, 96%), mp 238-239°; ir: ν cm^{-1} 3050, 2940, 1730, 1658, 1595; ms: m/z 407 (M^+), 409 (M^+ +2); pmr: 9.35 (s, 1H), 7.92 (s, 2H), 7.73 (s, 1H) (C_{3a}-H, C_6-H, C_7-H and C_9-H), 3.85 (s, 4H, CH_2-N-CH_2), 3.78 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 3.52 (s, 4H, CH_2-O-CH_2).

Calcd. for $C_{18}H_{18}ClN_3O_6$: 407.088 (M^+), 409.085 (M^+ +2). Found: 407.085 (M^+), 409.082 (M^+ +2).

8-Chloro-1,2,3-trismethoxycarbonyl-4-(piperidin-1-yl)pyrrolo-[1,2-*a*]quinoxaline **12a** and 8-Chloro-1,2,3-trismethoxycarbonyl-4-(morpholin-4-yl)pyrrolo[1,2-*a*]quinoxaline **12b**.

A solution of **10a** (2 g, 7.6 mmoles) or **10b** (2 g, 7.6 mmoles) and dimethyl acetylenedicarboxylate (2.35 g, 16.7 mmoles) in dioxane (60 ml) was refluxed in an oil bath for 6 hours. Removal of the solvent *in vacuo* afforded crystals, which were triturated with ethanol/hexane and then collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/water provided colorless needles **12a** (1.06 g, 30%) or **12b** (0.94 g, 27%).

Compound **12a**.

This compound had mp 152-153°; ir: ν cm^{-1} 3120, 2940, 1730, 1710, 1598; ms: m/z 459 (M^+), 461 (M^+ +2); pmr: 7.69 (d, J = 2.0 Hz, 1H, C_9-H), 7.68 (d, J = 9.0 Hz, 1H, C_6-H), 7.53 (dd, J = 2.0 Hz, J = 9.0 Hz, 1H, C_7-H), 4.02 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 3.28 (s, 4H, CH_2-N-CH_2), 1.58 (s, 6H, CH_2-CH_2-CH_2).

Anal. Calcd. for $C_{22}H_{22}ClN_3O_6$: C, 57.46; H, 4.82; Cl, 7.71; N, 9.14. Found: C, 57.53; H, 4.85; Cl, 8.01; N, 9.25.

Compound **12b**.

This compound had mp 164-166°; ir: ν cm^{-1} 3110, 2950, 1725, 1710, 1598; ms: m/z 461 (M^+), 463 (M^+ +2); pmr: 7.72 (d, J = 9.0 Hz, 1H, C_6-H), 7.71 (d, J = 2.5 Hz, 1H, C_9-H), 7.57 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H, C_7-H), 4.04 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 3.70 (t, J = 4.5 Hz, 4H, CH_2-N-CH_2), 3.29 (t, J = 4.5 Hz, 4H, CH_2-O-CH_2).

Anal. Calcd. for $C_{21}H_{20}ClN_3O_7$: C, 54.61; H, 4.37; Cl, 7.68; N, 9.10. Found: C, 54.54; H, 4.39; Cl, 7.68; N, 9.22.

Ring Transformation of **11a,b** into **12a,b**.

A solution of **11a** or **11b** (2 g) and dimethyl acetylenedicarboxylate (0.77 g, 1.1-fold) in dioxane (60 ml) was refluxed in an oil bath for 7 hours. Removal of the solvent *in vacuo* afforded crystals, which were triturated with ethanol and then collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/water gave colorless needles **12a** (0.45 g, 20%) or **12b** (0.75 g, 33%).

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