A Convenient Synthesis of Novel Pyridazino[3,4-*b*]quinoxaline and Pyrazolo[3,4-*b*]quinoxaline Utilizing 1,3-Dipolar Cycloaddition Reaction

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The reaction of 2,6-dichloroquinoxaline 4-oxide **4** with methylhydrazine gave 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **5**, whose reaction with dimethyl acetylenedicarboxylate or 2-chloroacrylonitrile resulted in the 1,3-dipolar cycloaddition reaction to afford 7-chloro-3,4-bismethoxycarbonyl-1-methyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline **6** or 6-chloro-3-hydroxymethylene-1-methyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]-quinoxaline hydrochloride **7**, respectively.

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In a previous paper [2], we reported that the reaction of the quinoxaline *N*-oxide **1a** or **1b** with dimethyl acetylenedicarboxylate (DMAD) effected the 1,3-dipolar cycloaddition reaction to give the isoxazolo[2,3-*a*]quinoxaline **2a** or **2b**, respectively, whose further reaction with DMAD resulted in ring transformation to provide the pyrrolo[1,2-*a*]-quinoxaline **3a** or **3b**, respectively (Chart 1). These results suggested that an intermediary isoxazolo[2,3-*a*]quinoxaline was rather labile and able to be transformed into various quinoxaline derivatives. When an amino group was installed in an intermediary isoxazolo[2,3-*a*]quinoxaline **I** as shown in Chart 2, the isoxazole ring opening and subsequent cyclization would be facilitated to produce the linear type of condensed quinoxaline **III** *via* an open-chained intermediate **II**. Accordingly, the model system shown in Chart 2 was devised so as to generate an intermediate **I** in the present investigation, and the practice of this experiment conveniently furnished novel pyridazino-[3,4-*b*]quinoxaline **6** (Scheme 1) and pyrazolo[3,4-*b*]quinoxaline **7** (Scheme 2). This paper describes a facile synthesis of 7-chloro-3,4-bismethoxycarbonyl-1-methyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline **6** and 6-chloro-3-hydroxymethylene-1-methyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]quinoxaline hydrochloride **7** *via* the 1,3-dipolar cycloaddition reaction.

The reaction of 2,6-dichloroquinoxaline 4-oxide **4** [2] with methylhydrazine gave 6-chloro-2-(1-methylhydrazino)-quinoxaline **5**, whose reaction with DMAD afforded the pyridazino[3,4-*b*]quinoxaline **6** presumably *via* intermediates **A** and **B** [2] (Scheme 1). On the other hand, the reaction of **5** with 2-chloroacrylonitrile provided the pyrazolo[3,4-*b*]quinoxaline hydrochloride **7** presumably *via* intermediates **C**, **D** and **E** [3] (Scheme 2). An attempt to isolate the isoxazolo[2,3-*a*]quinoxalines **A** and **C** was un-

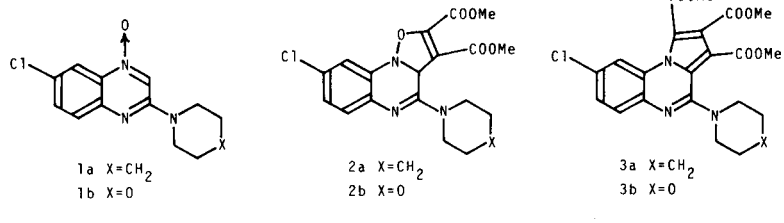


Chart 1

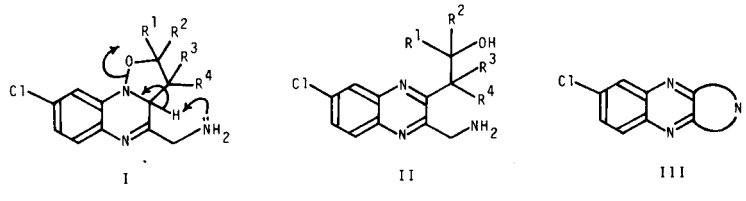
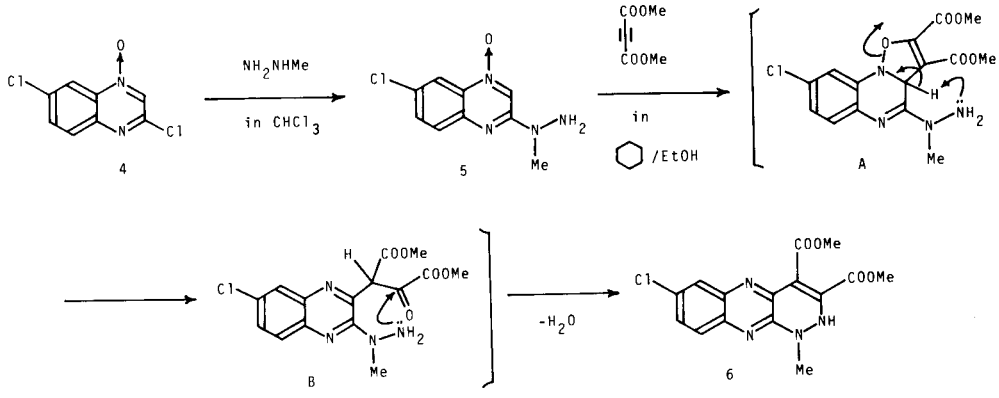
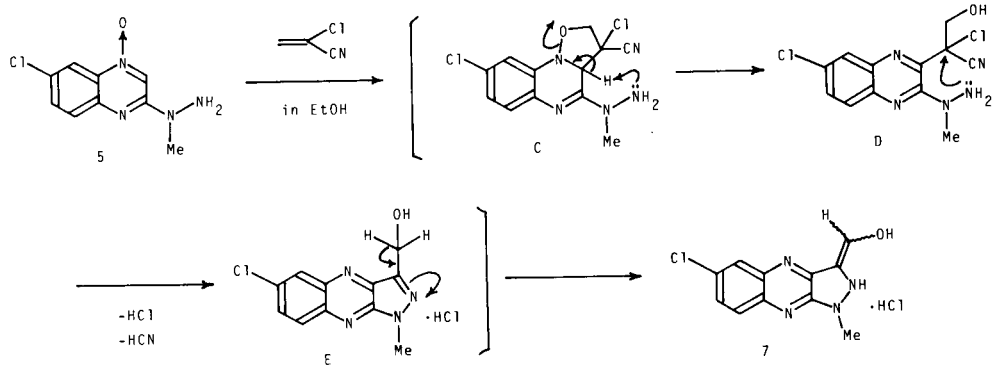


Chart 2

Scheme 1



Scheme 2



successful presumably due to the rapid isoxazole ring opening accelerated by the hydrazino group.

The structural assignment of **5**, **6** and **7** was based on the analytical and spectral data. Since the pmr spectrum of **7** showed three active protons at δ 11.70, 10.72 and 10.61 ppm, an intermediate **E** (Scheme 2) was found to isomerize into **7**. The olefinic proton of **7** was observed at δ 5.69 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 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 δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

6-Chloro-2-(1-methylhydrazino)quinoxaline 4-Oxide **5**.

A solution of 2,6-dichloroquinoxaline 4-oxide **4** (10 g, 46.5 mmoles) and methylhydrazine (6.44 g, 140 mmoles) in chloroform (200 ml) was refluxed on a boiling water bath for 2 hours to give a clear solution. Successively, ethanol (100 ml) was added to the solution with heating. The hot solution was filtered to precipitate analytically pure yellow needles **5**, which were collected by suction filtration (7.72 g). The filtrate was evaporated *in vacuo* to give yellow crystals, which were recrystallized from ethanol/water to afford yellow needles **5** (1.69 g), total yield, 8.41 g (81%). Compound **5** had mp 223-224°; ir: ν cm^{-1} 3290, 3100, 1610; ms: m/z 224 (M^+), 226 ($M^+ + 2$); pmr: 8.60 (s, 1H, C_3-H), 8.14 (d, J = 2.5 Hz, 1H, C_5-H), 7.63 (dd, J = 2.5 Hz, J = 9.0 Hz, 1H, C_7-H), 7.57 (d, J = 9.0 Hz, 1H, C_8-H), 4.99 (s, 2H, NH_2), 3.31 (s, 3H, CH_3).

Anal. Calcd. for $C_9H_9ClN_4O$: C, 48.12; H, 4.04; Cl, 15.78; N, 24.94. Found: C, 48.26; H, 4.05; Cl, 15.98; N, 24.72.

7-Chloro-3,4-bismethoxycarbonyl-1-methyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline **6**.

A solution of **5** (5 g, 22.3 mmoles) and dimethyl acetylenedicarboxylate (3.8 g, 26.7 mmoles) in cyclohexane (250 ml)/ethanol (100 ml) was refluxed on a boiling water bath for 3 hours to precipitate analytically pure orange needles **6**, which were collected by suction filtration (4.54 g). The filtrate was evaporated *in vacuo* to give orange needles **6**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (0.17 g), total yield, 4.71 g (61%). Compound **6** had mp 172-173°; ir: ν cm^{-1} 3150, 2940, 1735, 1660, 1595; ms: m/z 348 (M^+), 350 ($M^+ + 2$); pmr: 9.90 (br s, 1H, NH), 7.20 (d, J = 2.5 Hz, 1H, C_6-H), 6.82 (dd, J = 2.5 Hz, J = 8.5 Hz, 1H, C_8-H), 6.71 (d, J = 8.5 Hz, 1H, C_9-H), 3.71 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.13 (s, 3H, NCH_3).

Anal. Calcd. for $C_{15}H_{13}ClN_4O_4$: C, 51.66; H, 3.76; Cl, 10.16; N, 16.03. Found: C, 51.54; H, 3.88; Cl, 10.31; N, 16.21.

6-Chloro-3-hydroxymethylene-1-methyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]quinoxaline Hydrochloride **7**.

A solution of **5** (5 g, 22.3 mmoles) and 2-chloroacrylonitrile (3.51 g, 40.1 mmoles) in ethanol (350 ml) was refluxed on a boiling water bath for 6 hours to precipitate analytically pure yellow needles **7**, which were collected by suction filtration (5.60 g, 88%). Compound **7** had mp above 310°; ir: ν cm^{-1} 3020, 2780, 1640, 1625, 1610, 1590; ms: m/z 248 (M^+), 250 ($M^+ + 2$); pmr: 11.70 (br s, 1H), 10.72 (s, 1H), 10.61 (br s, 1H), (NH, $-\overset{+}{N}H=$, OH), 7.02 (d, J = 8.5 Hz, 1H, C_8-H), 6.80 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H, C_7-H), 6.59 (d, J = 2.0 Hz, 1H, C_5-H), 5.69 (s, 1H, olefinic H), 3.55 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_9ClN_4O \cdot HCl$: C, 46.34; H, 3.54; Cl, 24.87; N, 19.65. Found: C, 46.59; H, 3.67; Cl, 24.78; N, 19.53.

REFERENCES AND NOTES

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