Synthesis of Pyridazino[3,4-*b*]quinoxalines and Pyrazolo[3,4-*b*]-quinoxaline by 1,3-Dipolar Cycloaddition Reaction [1]

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The pyridazino[3,4-*b*]quinoxalines **6a,b** and pyrazolo[3,4-*b*]quinoxaline hydrochloride **9** were synthesized by the 1,3-dipolar cycloaddition reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **5** with dimethyl or diethyl acetylenedicarboxylate and 2-chloroacrylonitrile, respectively. The reaction mechanisms were postulated for the formation of **6a,b** and **9**.

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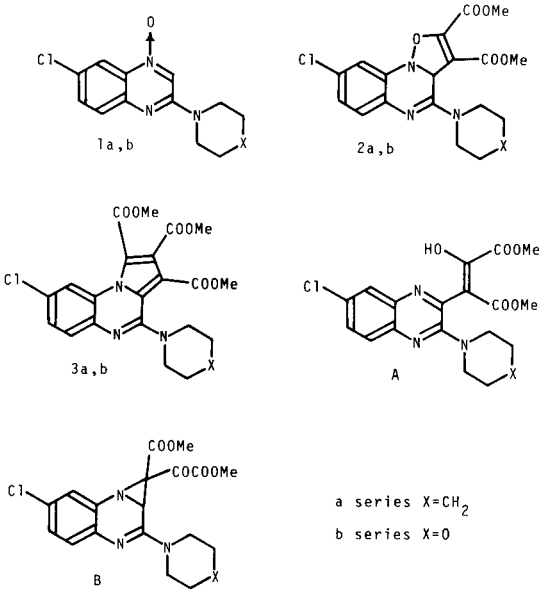
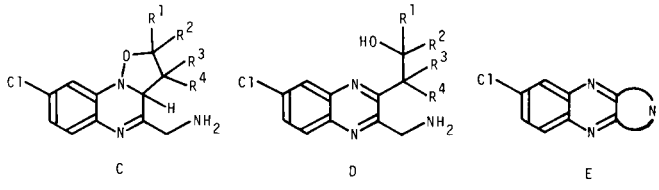
In a previous paper [3], we reported that the reaction of the quinoxaline *N*-oxide **1a** or **1b** with dimethyl acetylenedicarboxylate (DMAD) resulted in the 1,3-dipolar cycloaddition reaction to give the isoxazolo[2,3-*a*]quinoxaline **2a** or **2b**, respectively, whose further reaction with DMAD effected ring transformation to afford the pyrrolo[1,2-*a*]-quinoxaline **3a** or **3b**, respectively (Chart 1). For these ring

Chart 1



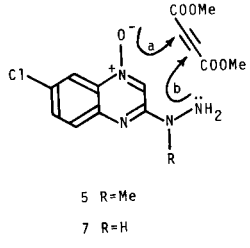
transformations, we proposed [4] that the reactions occurred *via* an isoxazole ring-opened intermediate **A** [5] and *via* an aziridine intermediate **B** [6-9]. The above results showed that an intermediate isoxazolo[2,3-*a*]quinoxaline underwent thermal isomerization at a relatively high temperature. However, when the isoxazolo[2,3-*a*]-quinoxaline intermediate **C** possessed an amino group on its side chain as shown in Chart 2, the isoxazole ring opening would be facilitated to give an open-chained intermediate **D** even at a relatively low temperature. Subsequently, the cyclization between the amino group and the

Chart 2



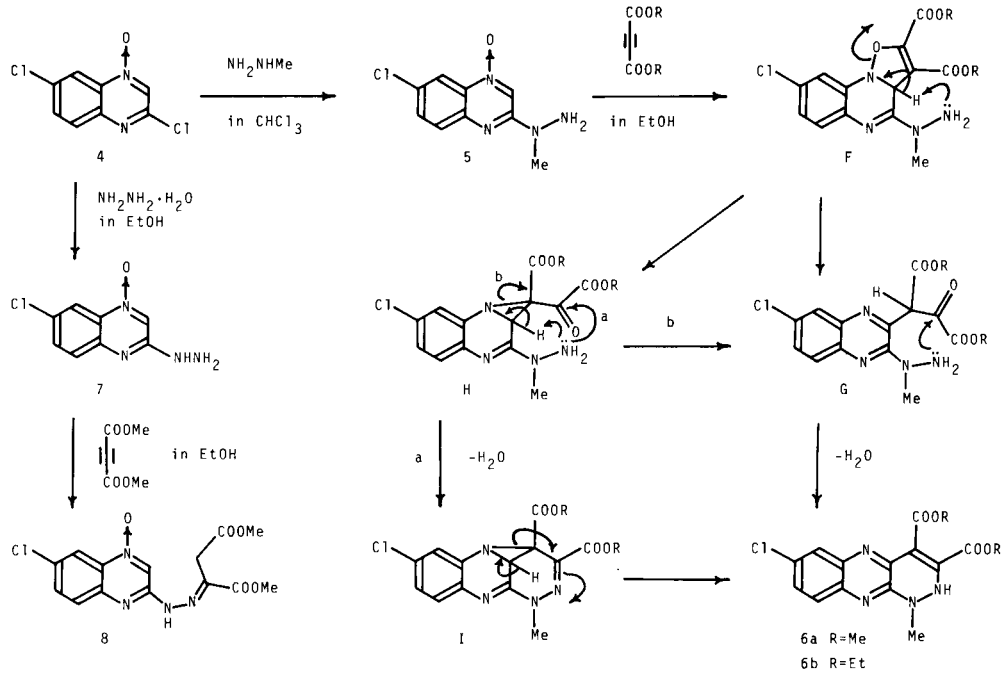
side chain of intermediate **D** would produce a linearly condensed quinoxaline **E**. Accordingly, for the present investigation, 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide (**5**) and 6-chloro-2-hydrazinoquinoxaline 4-oxide (**7**) were selected as starting materials from which to generate an intermediate **C**. Hereupon, the reaction of **5** with DMAD was found to result in a 1,3-dipolar cycloaddition reaction a, as depicted in Chart 3 giving the pyridazino-[3,4-*b*]quinoxaline **6a** (Scheme 1), while the reaction of **7**

Chart 3

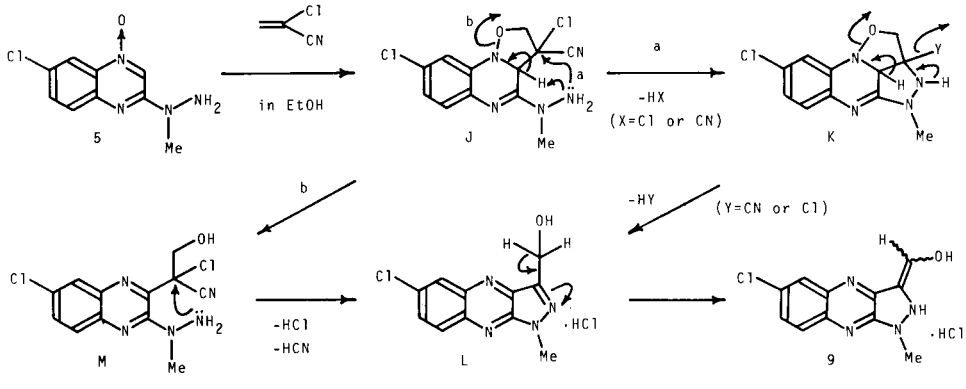


with DMAD effected the addition reaction b with the hydrazino moiety to yield **8**. The difference in the reactivity between **5** and **7** with DMAD may be due to the differences in the inductive effect of the two substitutent groups. The methylhydrazino group of **5** is stronger in electron donating effect to the aromatic ring than the hydrazino group of **7** [10]. As a result, the 1,3-dipolar cyclo-

Scheme 1



Scheme 2



addition reaction was predominant with compound **5**. Moreover, the reaction of **5** with 2-chloroacrylonitrile was found to result in a 1,3-dipolar cycloaddition reaction, producing the pyrazolo[3,4-*b*]quinoxaline hydrochloride **9** (Scheme 2). This paper describes a convenient synthesis of the pyridazino[3,4-*b*]quinoxalines **6a,b** and pyrazolo[3,4-*b*]quinoxaline **9** together with the proposed reaction mechanisms.

The reaction of 2,6-dichloroquinoxaline 4-oxide (**4**) [11] with methylhydrazine or hydrazine hydrate gave compound **5** or **7**, respectively. The reaction of **5** with DMAD or diethyl acetylenedicarboxylate afforded 7-chloro-3,4-bis(methoxycarbonyl)-1-methyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline (**6a**) or 7-chloro-3,4-bis(ethoxycarbonyl)-1-methyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline (**6b**), respectively, presumably *via* intermediates **F-I** (Scheme 1). The isoxazoline ring opening in an intermediate **F** would furnish **G** [5], while the thermal isomerization of the isoxazoline ring in intermediate **F** would provide a different intermediate aziridine **H** [6-9]. The dehydration (route a) or aziridine ring opening (route b) of intermediate **H** would give intermediate **I** or **G**, respectively. On the other hand, the reaction of **7** with DMAD produced dimethyl-(6-chloro-4-oxoquinoxalin-2-yl)hydrazonosuccinate (**8**).

The reaction of **5** with 2-chloroacrylonitrile produced 6-chloro-3-hydroxymethylene-1-methyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]quinoxaline hydrochloride **9** presumably *via* intermediates **J-M** (Scheme 2). The elimination of hydrogen chloride or cyanide in an intermediate **J** would follow route a to afford an intermediate **K**, while the isoxazolidine ring opening in an intermediate **J** would follow the route b to form an intermediate **M**. The isoxazolidine

ring opening and elimination of hydrogen cyanide or chloride from intermediate **K** would furnish the intermediate **L**, while the elimination of hydrogen chloride and hydrogen cyanide [12] from **M** would also give intermediate **L**. Since the pmr spectrum of **9** showed three active proton signals at δ 11.70, 10.72 and 10.61 ppm, we propose that intermediate **L** later isomerized to **9**. The olefinic proton signal of **9** 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, unless otherwise stated, 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. Ethanol (100 ml) was subsequently added to the solution with heating. The hot solution was filtered to precipitate analytically pure yellow needles of **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 additional yellow needles of **5** (1.69 g), total yield 8.41 g (81%), 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-bis(methoxycarbonyl)-1-methyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline (**6a**).

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 of **6a**, which were collected by suction filtration (4.54 g). The filtrate was evaporated *in vacuo* to give additional orange needles of **6a**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (0.17 g), total yield, 4.71 g (61%), mp 172-173°; ir: ν cm^{-1} 3150, 2940, 1735, 1660, 1595; ms: m/z 348 (M^+), 350 (M^++2); pmr: 9.90 (brs, 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.

7-Chloro-3,4-bis(ethoxycarbonyl)-1-methyl-1,2-dihydropyridazino[3,4-*b*]quinoxaline (**6b**).

A solution of **5** (2 g, 8.92 mmoles) and diethyl acetylenedicarboxylate (1.82 g, 10.7 mmoles) in ethanol (200 ml) was refluxed on a boiling water bath for 5 hours to give a clear solution. Evaporation of the solvent *in vacuo* gave yellow needles of **6b**, which were collected by suction filtration (1.77 g). Trituration with ethanol/*n*-hexane provided an analytically pure sample. Evaporation of the filtrate afforded yellow needles of **6b**, which were triturated with *n*-hexane and then collected by suction filtration (0.34 g), total yield, 2.11 g (63%), mp 162-163°; ir: ν cm^{-1} 1745, 1665, 1600; ms: m/z 376 (M^+), 378 (M^++2); pmr: 10.35 (s, 1H, NH), 7.17 (d, J = 2.5 Hz, 1H, C_6-H), 6.81 (dd, J = 2.5 Hz, J = 8.5 Hz, 1H, C_8-H), 6.70 (d, J = 8.5 Hz, 1H, C_9-H), 4.17 (q, J = 7.0 Hz, 2H, CH_2), 4.15 (q, J = 7.0 Hz, 2H, CH_2), 3.13 (s, 3H, CH_3), 1.25 (t, J = 7.0 Hz, 3H, CH_3), 1.19 (t, J = 7.0 Hz, 3H, CH_3).

Anal. Calcd. for $C_{17}H_{17}ClN_4O_4$: C, 54.19; H, 4.55; Cl, 9.41; N, 14.87. Found: C, 53.95; H, 4.49; Cl, 9.63; N, 14.87.

6-Chloro-2-hydrazinoquinoxaline 4-Oxide (**7**).

A solution of **4** (10 g, 46.5 mmoles) and hydrazine hydrate (7.0 g, 140 mmoles) in ethanol (500 ml) was refluxed on a boiling water bath for 2 hours to precipitate yellow needles of **7**. After water (100 ml) was added to the reaction mixture, the analytically pure yellow needles of **7** were collected by suction filtration, (6.62 g, 67%), mp 211-212°; ir: ν cm^{-1} 3320, 3240, 3060, 1595, 1565, 1510; ms: m/z 210 (M^+), 212 (M^+ +2); pmr: 8.67 (s, 1H, NH), 8.16 (s, 1H, C_3-H), 8.16 (d, J = 2.5 Hz, 1H, C_5-H), 7.66 (dd, J = 2.5 Hz, J = 9.0 Hz, 1H, C_7-H), 7.60 (d, J = 9.0 Hz, 1H, C_8-H), 4.54 (s, 2H, NH_2).

Anal. Calcd. for $C_8H_7ClN_4O$: C, 45.62; H, 3.35; Cl, 16.83; N, 26.60. Found: C, 45.72; H, 3.31; Cl, 17.04; N, 26.40.

Dimethyl (6-Chloro-4-oxoquinoxalin-2-yl)hydrazonosuccinate (**8**).

A solution of **7** (5 g, 23.8 mmoles) and dimethyl acetylenedicarboxylate (4.06 g, 28.6 mmoles) in cyclohexane (150 ml)/ethanol (350 ml) was refluxed on a boiling water bath for 3 hours whereupon colorless needles of **8** precipitated. The product was collected by suction filtration (3.65 g, 44%). Recrystallization from *N,N*-dimethylformamide/ethanol gave colorless needles, mp 234-235°; ir: ν cm^{-1} 3230, 3080, 2945, 1725, 1680; ms: m/z 352 (M^+), 354 (M^++2); pmr (deuteriochloroform): 12.37 (s, 1H, NH), 8.69 (s, 1H, C_3-H), 8.46 (d, J = 2.5 Hz, 1H, C_5-H), 7.75 (d, J = 9.0 Hz, 1H, C_8-H), 7.64 (dd, J = 2.5 Hz, J = 9.0 Hz, 1H, C_7-H), 3.87 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.58 (s, 2H, CH_2).

Anal. Calcd. for $C_{14}H_{13}ClN_4O_5$: C, 47.67; H, 3.71; Cl, 10.05; N, 15.88. Found: C, 47.56; H, 3.75; Cl, 10.06; N, 15.64.

6-Chloro-3-hydroxymethylene-1-methyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]quinoxaline Hydrochloride (**9**).

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 of **9**, which were collected by suction filtration (5.60 g, 88%), mp >310°; ir: ν cm^{-1} 3020, 2780, 1640, 1625, 1610, 1590; ms: m/z 248 (M^+), 250 (M^++2); pmr: 11.70 (brs, 1H), 10.72 (s, 1H), 10.61 (brs, 1H) (NH, -NH=, 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 $C_{11}H_9ClN_4O$·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.

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