Reaction of 6-Chloro-2-[1-methyl-2-(*N*-methylthiocarbamoyl)]-hydrazinoquinoxaline 4-Oxide with Dimethyl Acetylenedicarboxylate

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The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **4a** with methyl or phenyl isothiocyanate gave 6-chloro-2-[1-methyl-2-(*N*-methylthiocarbamoyl)hydrazino]quinoxaline 4-oxide **7a** or 6-chloro-2-[1-methyl-2-(*N*-phenylthiocarbamoyl)hydrazino]quinoxaline 4-oxide **7b**, respectively, whose reaction with dimethyl acetylenedicarboxylate afforded 6-chloro-2-[*N*-methyl-*N*-(5-methoxycarbonylmethylene-3-methyl-4-oxo-2-thioxoimidazolidin-1-yl)]aminoquinoxaline 4-oxide **8a** or 6-chloro-2-[*N*-methyl-*N*-(5-methoxycarbonylmethylene-4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl)]aminoquinoxaline 4-oxide **8b**, respectively.

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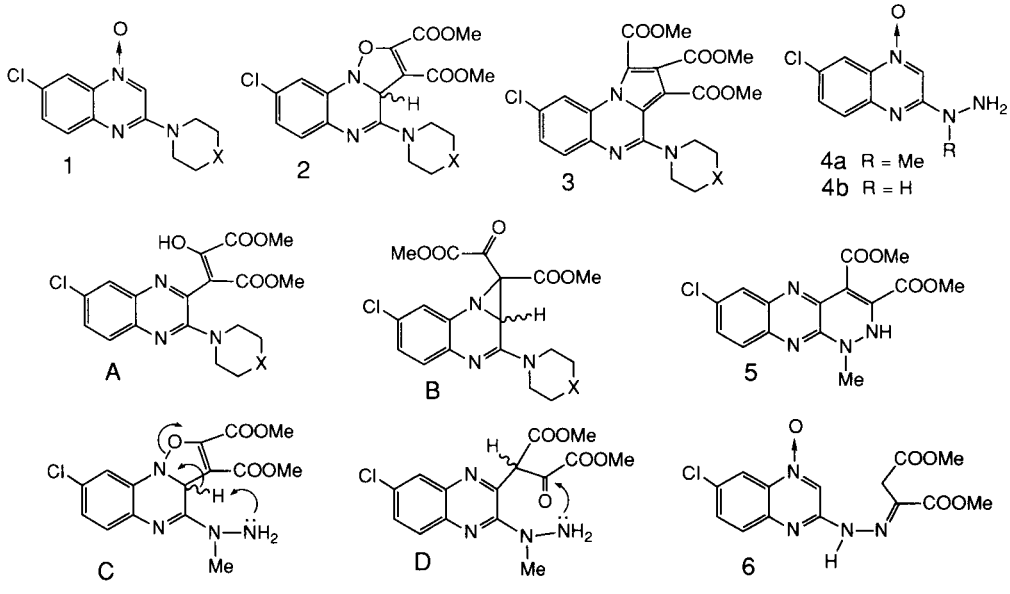
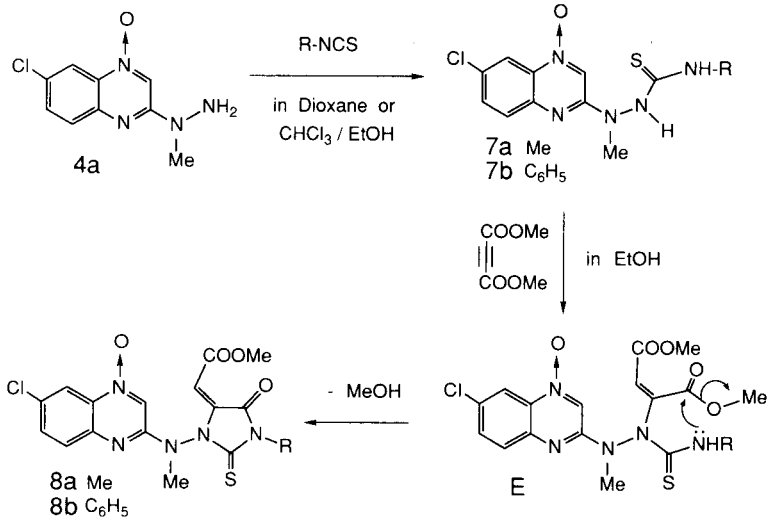
In previous papers [1-3], we reported that the 1,3-dipolar cycloaddition reaction of the quinoxaline 4-oxides **1** with an equimolar amount of dimethyl acetylenedicarboxylate under reflux in cyclohexane precipitated the isoxazolo-[2,3-*a*]quinoxalines **2**, whose reaction with another dimethyl acetylenedicarboxylate under reflux in dioxane resulted in ring transformation to afford the pyrrolo[1,2-*a*]quinoxalines **3** presumably *via* an intermediate **A** [1,2] and/or **B** [3] (Chart 1). The pyrrolo[1,2-*a*]quinoxalines **3** were also obtained directly even in the reaction of the quinoxaline 4-oxides **1** with an equimolar amount of dimethyl acetylenedicarboxylate under reflux in dioxane. In this case, the intermediary isoxazolo[2,3-*a*]quinoxalines **2** were soluble in dioxane, and hence these intermediates **2** immediately reacted with another dimethyl acetylenedicarboxylate to change into the pyrrolo[1,2-*a*]quinoxalines **3**. On the other hand, we found that the reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **4a** with an equimolar amount of dimethyl acetylenedicarboxylate effected the 1,3-dipolar cycloaddition reaction to provide the pyridazino[3,4-*b*]-

Chart 1



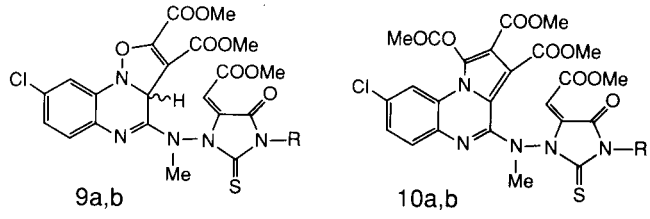
Scheme 1



quinoxaline **5** presumably *via* an intermediate **C** and then **D** [4], while the reaction of 6-chloro-2-hydrazinoquinoxaline **4b** with an equimolar amount of dimethyl acetylenedicarboxylate furnished the hydrazone **6** [5]. In case of compounds **4a** and **4b**, the presence or absence of the C_2-(N_1-methyl) group would excert an influence on the reactivity of the *N*-oxide moiety to dimethyl acetylenedicarboxylate. Moreover, the presence of the C_2-(N_1-methyl)hydrazino group in an intermediate **C** or **D** promoted the intramolecular dehydration taking precedence over the reaction of an intermediate **C** or **D** with another dimethyl acetylenedicarboxalate to form a pyrrolo[1,2-*a*]quinoxaline ring. The above results showed that an alteration of the C_2-substituent in the quinoxaline 4-oxides varied both the reactivity of the *N*-oxide moiety to a dipolarophile and the pathway of an intermediary isoxazolo[2,3-*a*]quinoxaline. In the present investigation, we further examined how the reactivity of the *N*-oxide moiety to dimethyl acetylenedicarboxylate was changed when the C_2-moiety of compound **4a** was transformed into a new type of substituent such as a thiosemicarbazide group. Thus, compound **4a** was converted into novel C_2-substituted quinoxaline 4-oxides **7a,b** (Scheme 1). In contrast to the case of compound **4a**, the reaction of compounds **7a,b** with an equimolar amount of dimethyl acetylenedicarboxylate was found to result in no 1,3-dipolar cycloaddition reaction in spite of the presence of the C_2-(N_1-methyl) group, but to form a imidazolidine ring in the C_2-side chain giving compounds **8a,b** (Scheme 1). However, the *N*-oxide moiety of compounds **8a,b** was clarified to be the most active site in the reaction with another dimethyl acetylenedicarboxylate. This paper mainly describes the synthesis of novel compounds **8a,b** together with their structural elucidation.

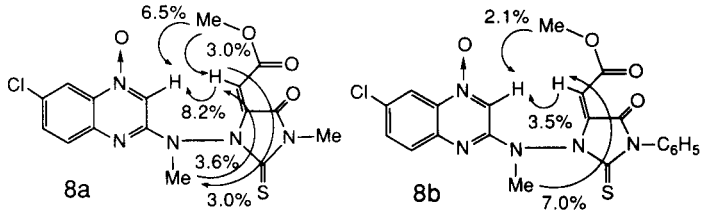
The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **4a** with methyl or phenyl isothiocyanate gave 6-chloro-2-[1-methyl-2-(*N*-methylthiocarbamoyl)hydrazino]-quinoxaline 4-oxide **7a** or 6-chloro-2-[1-methyl-2-(*N*-phenylthiocarbamoyl)hydrazino]quinoxaline 4-oxide **7b**, respectively, whose reaction with dimethyl acetylenedicarboxylate afforded 6-chloro-2-[*N*-methyl-*N*-(5-methoxycarbonylmethylene-3-methyl-4-oxo-2-thioxoimidazolidin-1-yl)]aminoquinoxaline 4-oxide **8a** or 6-chloro-2-[*N*-methyl-*N*-(5-methoxycarbonylmethylene-4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl)]aminoquinoxaline 4-oxide **8b**, respectively, presumably *via* an intermediate **E**. The reaction of compound **8a** or **8b** with dimethyl acetylenedicarboxylate in cyclohexane resulted in the 1,3-dipolar cycloaddition reaction to provide red needles of **9a** or **9b** (Chart 2), respectively. However, the mass spectrometry of the red needles were found to involve an impurity corresponding to compound **10a** or **10b**, and hence the clear analytical and spectral data were not obtained.

Chart 2



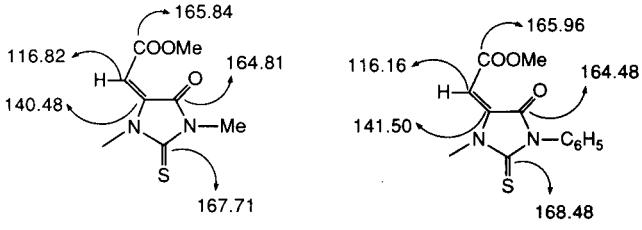
The structural assignment of compounds **7a,b** and **8a,b** was based on the analytical and spectral data. The ^{13}C-nmr spectra of compounds **7a** and **7b** showed the C=S carbon signals at δ 181.93 and 180.98 ppm, respectively, while the ^{13}C-nmr spectra of compounds **8a** and **8b** exhibited all the carbon signals at δ 169-29 ppm. The imidazolidine structure of **8a** and **8b** was supported by the NOE measurement among the C_2-(N_1-methyl), ester methyl, C_3-H and vinylic protons (Chart 3). Moreover, the LSPD spectrum of

Chart 3



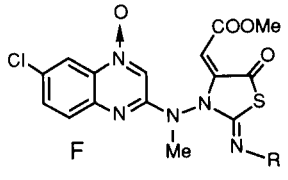
NOE Spectral Data for Compounds 8a,b

Chart 4



^{13}C-nmr Spectral Data in δ ppm

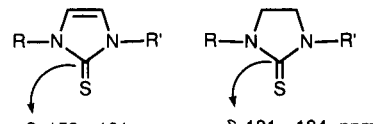
Chart 5



F

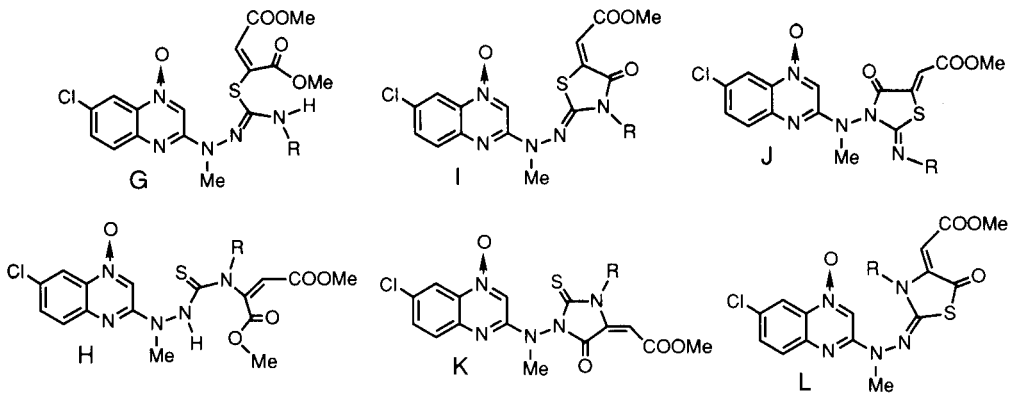
compound **8a** represented that the imidazolidine ring C=S and C=O carbon signals became singlet and doublet [^{3}J (vinylic H/C=O), 5.5 Hz], respectively, by a radiation at δ 3.35 ppm (ring N-methyl proton signal), that the ester C=O carbon signal became singlet by a radiation at δ 3.77 ppm (ester methyl proton signal) and that the imidazolidine ring C_5 and C=O carbon signals became singlet and quartet [^{3}J (ring N-methyl/C=O), 5.0 Hz], respectively, by a radiation at δ 6.86 ppm (vinylic proton signal). Thus, the above data provides no doubt for the imidazolidine ring, whose carbon signals are shown in Chart 4. Accordingly, the thiazolidine structure **F** (Chart 5) is excluded from the above LSPD spectral data. Faure *et al.* [6] have reported the various chemical shifts for the C=S carbons of the imidazoline-2-thiones and imidazolidine-2-thiones (Chart 6), indicating that the C=S carbon signals are not always observed in a lower magnetic field than δ 180 ppm. If an intermediate **G** or **H** (Chart 7) is formed by an

Chart 6



[Reference 6]

Chart 7



G I J H K L

initial attack of the thiocarbamoyl **S** or **N** to the acetylene carbon, the species **I,J** or **K,L** would be produced, respectively, by the subsequent cyclization. However, the structures **I-L** are inconsistent with the above NOE or LSPD spectral data.

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 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-methyl-2-(*N*-methylthiocarbamoyl)hydrazino]quinoxaline 4-Oxide **7a**.

A solution of compound **4a** (20 g, 89.1 mmoles) and methyl isothiocyanate (7.80 g, 106.9 mmoles) in dioxane (300 ml) was refluxed in an oil bath for 1 hour to precipitate yellow needles **7a**. After cooling to room temperature, the yellow needles **7a** were collected by suction filtration and washed with ethanol and then *n*-hexane to provide an analytically pure sample (17.26 g). Evaporation of the filtrate *in vacuo* afforded yellow crystals **7a**, which were collected by suction filtration and then washed with ethanol/*n*-hexane (5.51 g), total yield 22.78 g (86%).

Compound **7a** had mp 250-251°; ir: ν cm^{-1} 3260, 3200, 3140, 1670 1530; ms: m/z 297 (M^+), 299 ($M^+ + 2$); pmr: 9.83 (s, 1H, NH), 8.53 (q, J = 4.0 Hz, 1H, NH), 8.26 (s, 1H, C_3-H), 7.94 (s, 1H, C_5-H), 7.81 (s, 1H, C_7-H or C_8-H), 7.80 (s, 1H, C_8-H or C_7-H), 3.28 (s, 3H, N-CH_3), 2.92 (d, J = 4.0 Hz, 3H, N-CH_3).

Anal. Calcd. for $C_{11}H_{12}ClN_5OS$: C, 44.41; H, 4.07; Cl, 11.92; N, 23.54; S, 10.78. Found: C, 44.59; H, 4.10; Cl, 12.10; N, 23.25; S, 10.56.

6-Chloro-2-[1-methyl-2-(*N*-phenylthiocarbamoyl)hydrazino]quinoxaline 4-Oxide **7b**.

A solution of compound **4a** (10 g, 44.5 mmoles) and phenyl isothiocyanate (7.21 g, 53.4 mmoles) in chloroform (200 ml)/ethanol (100 ml) was refluxed on a boiling water bath for 1 hour. Evaporation of the solvent *in vacuo* gave yellow crystals **7b**, which were triturated with hot ethanol/*n*-hexane and then collected by suction filtration to provide an analytically pure sample (13.14 g). Evaporation of the filtrate *in vacuo* afforded yellow needles **7b**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (0.60 g), total yield 13.74 g (86%).

Compound **7b** had mp 275-276°; ir: ν cm^{-1} 3120, 1585, 1570, 1530, 1510; ms: m/z 359 (M^+), 361 ($M^+ + 2$); pmr: 10.20 (s, 2H, NH), 8.28 (s, 1H, C_3-H), 8.14 (s, 1H, C_5-H), 7.82 (s, 2H, C_7-H and C_8-H), 7.53 (d, J = 7.5 Hz, 2H, aromatic), 7.35 (dd, J = 7.5 Hz, J = 7.5 Hz, aromatic), 7.18 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H, aromatic), 3.38 (s, 3H, N-CH_3).

Anal. Calcd. for $C_{16}H_{14}ClN_5OS$: C, 53.41; H, 3.92; Cl, 9.85; N, 19.46; S, 8.91. Found: C, 53.62; H, 4.05; Cl, 9.63; N, 19.63; S, 9.12.

6-Chloro-2-[*N*-methyl-*N*-(5-methoxycarbonylmethylene-3-methyl-4-oxo-2-thioxoimidazolidin-1-yl)]aminoquinoxaline 4-Oxide **8a**.

A solution of compound **7a** (5 g, 33.6 mmoles) and dimethyl acetylenedicarboxylate (2.87 g, 40.3 mmoles) in ethanol (300 ml) was refluxed on a boiling water bath for 5 hours to precipitate yellow needles **8a**, which were collected by suction filtration and washed with ethanol and then *n*-hexane to provide an analytically pure sample (3.71 g, 54%), mp 223-224°; ir: ν cm^{-1} 1710, 1680, 1600, 1570, 1530; ms: m/z 407 (M^+), 409 ($M^+ + 2$); pmr: 8.49 (s, 1H, C_3-H), 8.27 (d, J = 2.1 Hz, 1H, C_5-H), 7.86 (d, J = 9.0 Hz, 1H, C_8-H), 7.80 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H, C_7-H), 6.86 (s, 1H, vinylic H), 3.76 (s, 3H, O-CH_3), 3.34 (s, 3H, N-CH_3), 3.33 (s, 3H, N-CH_3).

Anal. Calcd. for $C_{16}H_{14}ClN_5O_4S$: C, 47.16; H, 3.46; Cl, 8.71; N, 17.19; S, 7.87. Found: C, 47.16; H, 3.47; Cl, 8.97; N, 17.22; S, 7.61.

6-Chloro-2-[*N*-methyl-*N*-(5-methoxycarbonylmethylene-4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl)]aminoquinoxaline 4-Oxide **8b**.

A solution of compound **7b** (5 g, 13.9 mmoles) and dimethyl acetylenedicarboxylate (2.37 g, 16.7 mmoles) in ethanol (300 ml) was refluxed on a boling water bath for 5 hours to precipitate yellow prismic needles **8b**, which were collected by suction filtration and washed with ethanol/*n*-hexane to furnish an analytically pure sample (2.03 g, 31%), mp 219-220°; ir: ν cm^{-1} 1710, 1690; ms: m/z 469 (M^+), 471 ($M^+ + 2$); pmr: 8.35 (s, 1H, C_3-H), 8.25 (d, J = 2.0 Hz, 1H, C_5-H), 7.84 (d, J = 9.0 Hz, 1H, C_8-H), 7.78 (dd, J = 2.0 Hz, J = 9.0 Hz, 1H, C_7-H), 7.65 (d, J = 7.0 Hz, 2H, aromatic), 7.57 (dd, J = 7.0 Hz, J = 7.0 Hz, 2H, aromatic), 7.49 (dd, J = 7.0 Hz, J = 7.0 Hz, 1H, aromatic), 6.93 (s, 1H, vinylic H), 3.80 (s, 3H, O-CH_3), 3.30 (s, 3H, N-CH_3).

Anal. Calcd. for $C_{21}H_{16}ClN_5O_4S$: C, 53.68; H, 3.43; Cl, 7.54; N, 14.94; S, 6.82. Found: C, 53.77; H, 3.40; Cl, 7.81; N, 14.95; S, 6.71.

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