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The Reaction of 6,7-Dichloro-5,8-quinoxalinedione with Aromatic and Aliphatic Dinucleophiles and Molecular Modeling Study of Their Intercalation Complexes

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The angular and planar heterocyclic compounds containing nitrogen, sulfur and oxygen were synthesized by reaction of 6,7-dichloro-5,8-quinoxalinedione with aromatic and aliphatic dinucleophiles. Nucleophilic reactivity was somewhat different between 2,3-dichloro-1,4-naphthoquinone and 6,7-dichloro-5,8-quinolinedione with dinucleophiles. The distribution of electron in heterocycle appeared to contribute to this difference. The intercalation comple of planar heterocyclic compound between GC/GC base pairs showed the optimum intercalation but the intercalation of angular heterocyclic compound was not good. Thus, the planar compound was expected to have antitumor activity.

Introduction

The reaction of 2,3-dichloro-1,4-naphthoquinone and 6,7-dichloro-5,8-quinolinedione with nucleophiles was investigated for a long time. However, the reaction of the analogue 6,7-dichloro-5,8-quinoxalinedione (**1**) with nucleophiles was rarely reported because the total yield of **1** was only 1.1%.[1] The new method, in which the total yield was 27%, was developed recently.[2] Dichloro compound showed the diverse reactivity with nucleophiles and produced various heterocyclic compounds.[3] We synthesized heterocycles by reaction of **1** with aromatic and aliphatic dinu-

cleophiles containing nitrogen, sulfur and oxygen. The reactivity of **1** was compared to that of 2,3-dichloro-1,4-naphthoquinone and 6,7-dichloro-5,8-quinolinedione to examine the effect of nitrogen in the heterocycle. It had been reported the number of nitrogen in heterocycles and ring size were important for antitumor activity.[1] The derivatives of **1** had more than two nitrogens and 3-4 rings. Intercalation complexes between the derivatives and GC/GC base pairs were showed by molecular modeling for expecting antitumor activity.

Experimental

Materials and Methods. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 300 MHz Varian Gemini nmr spectrometer. Samples were dissolved in DMSO-d_6. Mass spectra were obtained on a Hewlett Packard 5790(70 eV) GC-Mass and GC-Mass 5985B. Elemental analyses were performed using Perkin-Elmer Model 240C elementary analyzer. IR spectra were recorded on a Perkin Elmer Model 1710 spectrometer and Mattson Instruments Inc.. The majority of reagents were purchased from Aldrich Chemical Company.

6-Chloro-5-hydroxy-12H-pyrazino[2,3-a]phenothiazine (3). 6,7-Dichloro-5,8-quinoxalinedione **(1)** (100 mg, 0.44 mmol) was dissolved in boiling ethanol (20 mL). 2-Aminothiophenol (0.07 mL, 0.53 mmol) was added to this hot solution and the reaction mixture was refluxed for 1 h. The solvent was evaporated under reduced pressure and ethanol was added to this residue. The precipitate was collected by filtration and loaded on a silica gel column (Kieselgel 9385, 230-400 mesh) eluted with chloroform/acetone (9 : 1): yield, 110 mg (84.6%); mp 222-225 °C; ^{1}H NMR δ 7.78 (m, 2H, *H*- 9,10), 8.06 (dd, 1H, J=not resolved, *H*- 11), 8.23 (dd, 1H, *H*- 8), 9.21 (dd, 1H, *H*- 2 or 3), 9.25 (dd, 1H, *H*- 2 or 3), 9.41 (s, 1H, *OH*), 10.65 (s, 1H, *NH*) ; IR (KBr) 3420, 3040 cm^{-1}; MS m/z for $C_{14}H_8N_3OS^{35}Cl$ 301; m/z for $C_{14}H_8N_3OS^{37}Cl$ 303.

6-Chloro-5-hydroxy-12H-pyrazino[2,3-a]phenoxazine (4). 6,7-Dichloro-5,8-quinoxalinedione (1) (100 mg, 0.44 mmol) was dissolved in boiling ethanol (20 mL). 2-Aminophenol (60 mg, 0.53 mmol) was added to this hot solution and the reaction mixture was refluxed for 1 h. The solvent was evaporated under reduced pressure and ethanol was added to the residue. The precipitate was collected by filtration: yield, 100 mg (83.3%); mp 223-225 °C; ^{1}H NMR δ 7.11 (m, 2H, *H*- 9,10), 7.20 (dd, 1H, *J* =5.85 Hz, *H*- 8), 7.53 (dd, 1H, *J* =5.98 Hz, *H*- 11), 8.56 (s, 1H, *OH*), 8.98 (s, 2H, *H*- 2,3), 10.86 (s, 1H, *NH*); IR (KBr) 3480 cm^{-1}; MS *m z* for $C_{14}H_8N_3O_2^{35}Cl$ 477; *m z* for $C_{14}H_8N_3O_2^{37}Cl$ 479 (TFAA derivative).

6-Acetamido-7-(4-aminophenoxy)-5,8-quinoxalinedione (5). 4-Aminophenol (260 mg, 2.39 mmol) was added to a suspension of 6-acetamido-7-chloro-5,8-quinoxalinedione (300 mg, 1.3 mmol) in ethanol (20 mL) at 70 °C and the reaction mixture was refluxed for 30 min. After cooling, the precipitate was collected by filtration and recrystallized from ethanol: yield, 350 mg (89.7%); mp 184-186 °C; ^{1}H NMR δ 1.35 (s, 3H, $COCH_3$), 6.64 (d, 2H, *J* = 7.7 Hz, *H*- 3',5'), 6.81 (d, 2H, *J* =7.7 Hz, *H*- 2',6'), 8.98 (d, 2H, *H*- 2,3), 9.13 (s, 2H, *NH*), 9.37 (s, 1H, $NHCOCH_3$); IR (KBr) 3280, 3200, 1660, 1630 cm^{-1}.

2-Methoxy-6-chloro-5-hydroxy-12H-pyrazino[2,3-a]phenazine (6). 6,7-Dichloro-5,8-quinoxalinedione **(1)** (100 mg, 0.44 mmol) was dissolved in boiling ethanol (20 mL). 4-Methoxy-1,2-phenylenediamine · 2HCl (140 mg, 0.65 mmol) was added to this hot solution and the reaction mixture was refluxed for 30 min. After cooling, the precipitate was collected by filtration and recrystallized from ethanol: yield, 120 mg (85.7%); mp >300 °C; ^{1}H NMR δ 8.96 (s, 2H, *H*- 9,10), 7.99 (d, 1H, *H*- 1), 7.38 (d, 1H, *H*- 2), 7.01 (d, 1H, *H*- 4), 3.94 (s, 3H, OCH_3).

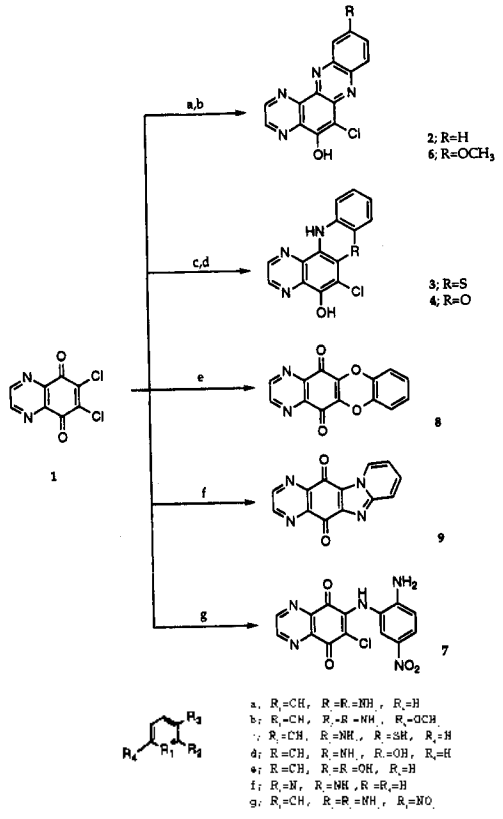
6-Chloro-7-(6-amino-3-nitrophenyl)amino-5,8-quinoxalinedione (7). 6,7-Dichloro-5,8-quinoxalinedione **(1)** (100 mg, 0.44 mmol) was dissolved in boiling ethanol (20 mL). 4-Nitro-1,2-phenylenediamine (100 mg, 0.66 mmol) was added to this hot solution and the reaction mixture was refluxed for 1 h. The solvent was evaporated under reduced pressure and ethyl acetate was added to the residue and then the precipitate was collected by filtration: yield, 90 mg (60%); mp 284-286 °C; ^{1}H NMR δ 7.67 (br. m, 1H, *H*- 4'), 8.25 (s, 1H, *H*- 5'), 8.94 (s, 2H, *H*- 2',2), 9.10 (s, 1H, *H*- 3), 10.6 (br. s, 2H, *H*).

Pyrazino[2,3-b]naphtho[2,3-e][1,4]dioxino-5,12-quinone (8). 6,7-Dichloro-5,8-quinoxalinedione **(1)** (100 mg, 0.44 mmol) was dissolved in boiling ethanol (20 mL). *o*- Catechol (60 mg, 0.53 mmol) and triethylamine were added to this hot solution and the reaction mixture was refluxed for 30 min. The solvent was evaporated under reduced pressure. The residue was loaded on a silica gel column (Kieselgel 9385, 230-400 mesh) eluted with chloroform/acetone (9 : 1): yield, 90 mg (75%); mp 210-211 °C; ^{1}H NMR δ 7.24 (m, 3H, *H*- 8,9 and 7 or 10), 7.31 (d, 1H, *J* = 7.68 Hz, *H*-7 or 10), 9.07 (dd, 2H, *J* =9.03 Hz, *H*- 2,3); IR (KBr) 1680 cm^{-1}; MS *m z* for $C_{14}H_6N_2O_4$ 266.

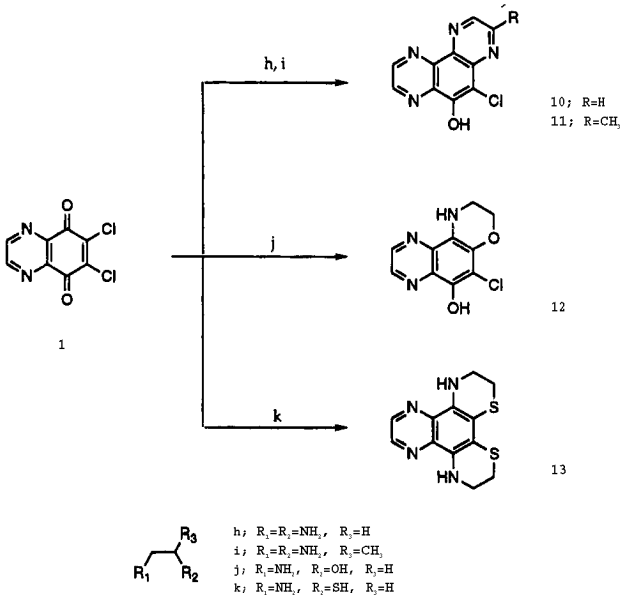
5-Chloro-6-hydroxypyrazino[2,3-h]quinoxaline (10). 6,7-Dichloro-5,8-quinoxalinedione **(1)** (300 mg, 1.32 mmol) was dissolved in acetonitrile (20 mL). Ethylenediamine (0.12 mL, 1.97 mmol) and diisopropylethylamine (0.69 mL, 3.95 mmol) were added to this solution and the reaction mixture was stirred for 10 min. The precipitate was collected by filtration and recrystallized from ethyl acetate/n-hexane: yield, 170 mg (61.3%); mp >280 °C; ^{1}H NMR δ 9.03 (d, 1H, *H*- 2 or 3), 9.13 (d, 1H, *H*- 2 or 3), 9.21 (d, 1H, *H*- 8 or 9), 9.27 (d, 1H, *H*- 8 or 9), 7.96 (s, 1H, *OH*); IR (KBr) 3350 cm^{-1}; MS *m z* for $C_{10}H_5N_4O^{35}Cl$ 232, 328 (TFAA derivative); *m z* for $C_{10}H_5N_4O^{37}Cl$ 234, 330 (TFAA derivative).

3-Methyl-5-chloro-6-hydroxypyrazino[2,3-h]quinoxaline (11). 1,2-Diaminopropane (0.18 mL, 1.97 mmol) was added to a suspension of 6,7-dichloro-5,8-quinoxalinedione **(1)** (300 mg, 1.32 mmol) in ethanol (20 mL) and this reaction mixture was stirred for 30 min. The solvent was evaporated under reduced pressure and ethanol and ethyl acetate were added to the residue. The precipitate was collected by filtration: yield, 190 mg (59.4%); mp >280 °C; ^{1}H NMR δ 3.33 (d, 3H, CH_3), 9.54 (m, 3H, *H*- 2,8,9); IR (KBr) 3230 cm^{-1}.

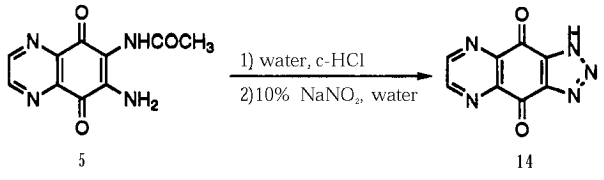
10-Chloro-9-hydroxy-4H-2,3-dihydropyrazino[2,3- *f*][1,4]benzoxazine (12). Monoethanolamine (0.12 mL, 1.97 mmol) was added to a suspension of 6,7-dichloro-5,8-quinoxalinedione **(1)** (300 mg, 1.32 mmol) in ethanol



Scheme 1.



Scheme 2.



Scheme 3.

(10 mL) and acetonitrile (10 mL) at 0 °C, and this reaction mixture was stirred for 1 h. The precipitate was collected by filtration and recrystallized from ethanol: yield, 230 mg (74.2%); mp 132-134 °C; ^{1}H NMR δ 3.48 (m, 1H, NCH_2), 3.88 (m, 2H, each H of N -*CH*$_2$-*CH*$_2$- O), 4.32 (m, 1H, OCH_2), 8.01 (s, 1H, *OH*), 8.52 (s, 1H, *NH*), 8.81 (dd, 2H, *H*- 6,7); IR (KBr) 3350 cm^{-1}; MS *m z* for $C_{10}H_8N_3O_2^{35}Cl$ 237; MS *m z* for $C_{10}H_8N_3O_2^{37}Cl$ 239.

4H-2,3-dihydropyrazino[2,3-a]9,10-dihydrothiazino[2,3-c][1,4]benzothiazin (13). A solution of 6,7-dichloro-5,8-quinoxalinedione **(1)** (300 mg, 1.32 mmol) in ethanol (5 mL) was added to a solution of aminoethanthiol · HCl (80 mg, 1.97 mmol) and triethylamine (0.07 mL) in ethanol (20 mL) under nitrogen and the reaction mixture was stirred for 30 min. The precipitate was collected by filtration and recrystallized from ethanol: yield, 190 mg (52.8%); mp 276-278 °C; ^{1}H NMR δ 3.27 (m, 4H, *SCH* $_2$), 4.03 (m, 4H, *NCH* $_2$), 8.82 (d, 1H, *H*- 10), 9.01 (d, 1H, *H*- 11), 10.2 (s, 1H, *NH*); IR (KBr) 3350 cm^{-1}; MS *m z* for $C_{12}H_{12}N_4S_2$ 276.

1H-Triazo[4,5-g]quinoxaline-4,9-dione (14). 6-Acetamido-7-amino-5,8-quinoxalinedione **(5)** (500 mg, 2.2 mmol) was dissolved in water (10 mL) with c-HCl (0.3 mL) and the color was removed with chlorite pad and the filtrate was diluted with water (20 mL). 10% $NaNO_2$ solution (20 mL) was added slowly to this solution at 10 °C with stirring over a period of 2 h. The solvent was evaporated under reduced pressure and ethanol was added to the residue and the precipitate was collected by filtration: yield, 280 mg (65.1%); mp 243-245 °C; ^{1}H NMR δ 8.98 (d, *H*- 2,3); IR (KBr) 2131, 1676 cm^{-1}.

Result and Discussion

The reaction of 6,7-dichloro-5,8-quinoxalinedione **(1)** with 1,2-phenylenediamine, 2-aminothiophenol and 2-aminophenol gave 6-chloro-5-hydroxy-12H-pyrazino[2,3-a] phenazine **(2),** 6-chloro-5-hydroxy-12H-pyrazino[2,3-a] phenothiazine **(3)** and 6-chloro-5-hydroxy-12H-pyrazino[2,3-a]phenoxazine **(4),** respectively which were angular heterocyclic compounds (Scheme 1). That yield of reaction was higher than with catalyst like cerium chloride hydrate.[4] Reaction mechanism could be both of nucleophilic substitution and nucleophilic addition.[3] Allan and Reynolds[5] reported that the condensation of 2,3-dichloro-1,4-naphtoquinone with 2-aminothiophenol produced 5,16-dithia-5, 10-diazanaphtho[2,3-a]benzo[c]anthracene which was condensation compound with 2 mole of 2-aminothiophenol. However, in the case of **1** even though more than 2 eq. of 2-aminothiophenol was introduced, the compound **3** was obtained. It was the same result as the reaction of **1** with 2-aminothiophenol. When **1** was treated with 2-aminophenol in ethanol, the enol form **4** was obtained. In this reaction the attack of amino group on carbon in 6-position was expected but hydroxyl group attacked to chlorine carbon for substitution and amino group was condensed with quinone. When 6-acetamido-7-chloro-5,8-quinoxalinedione was treated with 4-aminophenol to generalize it, 6-acetamido-7-(4-aminophenoxy)-5,8-quinoxaline dione **(5)** was obtained.

The effect of electron withdrawing and electron donating

substituents in 1,2-phenylenediamine on condensation was examined. The reaction of **1** with 4-methoxy-1,2-phenylenediamine gave condensation compound (**6**). But the ring closure compound was not able to obtain by reaction of **1** with 4-nitro-1,2-phenylenediamine because of the weak basicity of amine. Thus the nitro group which was an electron withdrawing group in 4-nitro-1,2-phenylenediamine completely inhibited ring closure.

The reaction of **1** with *o*-catechol produced a linear ring closure compound,[6] pyrazino[2,3-*b*]naphtho[2,3-*e*][1,4]dioxino-5,12-quinone (**8**). Triethylamine was necessary as a catalyst in this reaction.

As described previously[3] the reaction of **1** with 2-aminopyridine produced a linear heterocyclic compound, pyrido[1,2-*a*]imidazo[4,5-*g*]quinoxaline-6,11-dione (**9**) directly. This result was the same as 6,7-dichloro-5,8-quinolinedione but different from 2,3-dichloro-1,4-naphthoquinone.

The reaction of **1** with aliphatic dinucleophile yielded condensation products and showed diversity in the nature of the reaction (Scheme 2). Unexpectedly, 5-chloro-6-hydroxypyrazino[2,3-*h*]quinoxaline (**10**), which was an aromatized compound, was prepared by reaction of **1** with ethylenediamine[7] in the presence of diisopropylethylamine. The aromatization was not occurred in the reaction of 2,3-dichloro-1,4-naphthoquinone and 6,7-dichloro-5,8-quinolinedione with ethylenediamine. Many attempts to get an unaromatized condensation compound of **1** with ethylene diamine were tried under various conditions but compound **10** was obtained in every cases. The analogue reaction[7] of **1** with 1,2-diaminopropane gave an aromatized compound, 3-methyl-5-chloro-6-hydroxy-pyrazino[2,3-*h*]quinoxaline (**11**). However, the ring closure compound was not obtained by reaction of **1** with N-methylethylenediamine.

10-Chloro-9-hydroxy-4H-pyrazino[2,3-*f*]benzoxazine (**12**) was obtained by reaction of **1** with monoethanolamine.[8] Reaction of **1** with aminoethanthiol gaved a cyclization product, 4H-2,3-dihydropyrazino[2,3-*a*]9,10-dihydrothiazino[2,3-*c*][1,4]benzothiazine (**13**), in which both of the chlorine atoms were replaced by sulfur atom. The compound **13** might be formed via a Michael addition elimination reaction and subsequent ring closure through condensation reaction of amino group and ketone. This was a different result from the reaction of **1** with 2-aminothiophenol.

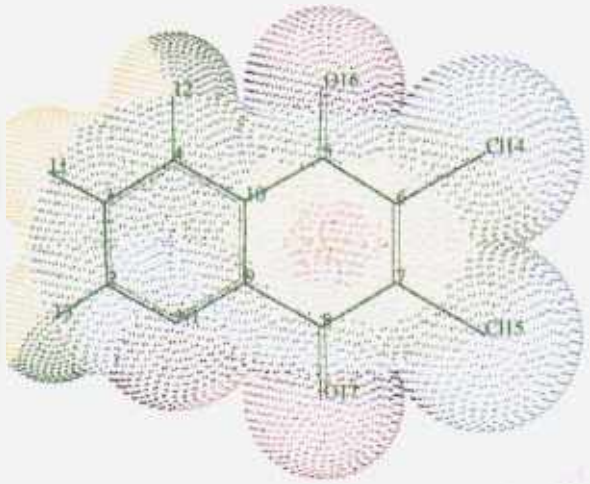


Figure 1. The electron distribution of 6,7-dichloro-5,8-quinolinedione: blue-violet, -charge; yellow; neutral; green; +charge.

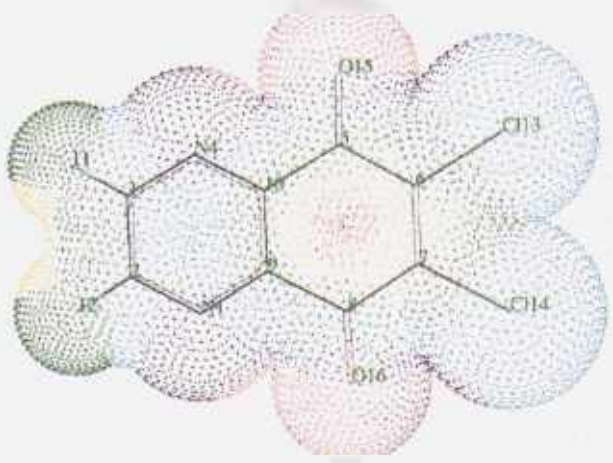


Figure 2. The electron distribution of 6,7-dichloro-5,8-quinoxalinedione (1): blue-violet; -charge; yellow; neutral; green; + charge.

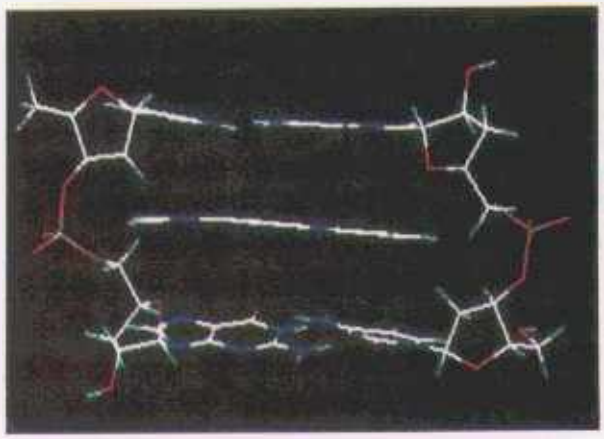


Figure 3. DNA intercalation complex of pyrido[1,2-*a*]imidazo[4,5-*g*]quinoxaline-6,11-dione (**9**) between GC/GC base pairs.

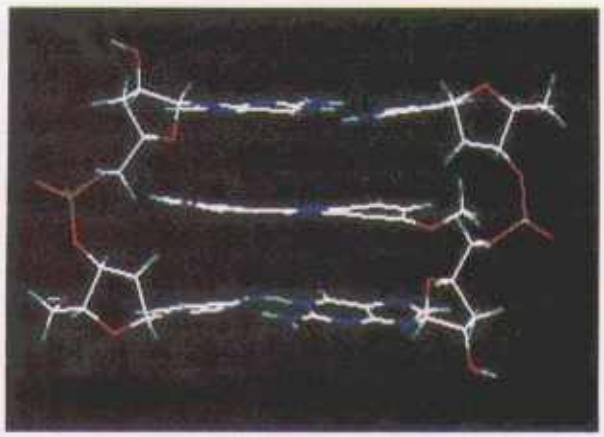


Figure 4. DNA intercalation complex of 2-methoxy-6-chloro-5-hydroxy-12H-pyrazino[2,3-*a*]phenazine (**6**) between GC/GC base pairs.

Diazotization[10] of 6-acetamido-7-amino-5,8-quinoxalinedione gave another ring closure compound, 1H-triazo[4,5-g]quinoxaline-4,9-dione **(14)** (Scheme 3). 6-Acetamido-7-amino-5,8-quinoxaline dione was synthesized from 6,7-diamino-5,8-quinoxalinedione.[6] Diaminoquinone was formed by amination of dichloroquinone with ammonia readily.[11] However, **1** reacted with ammonia to yield 6,7-dichloro-5,8-quinoxalinol which was a reducted compound.

The compound 1 showed the different reactivity from 2,3-dichloro-1,4-naphthoquinone and 6,7-dichloro-5,8-quinolinedione in some reactions. It was probably caused by electronic effects. A comparison of electron densities in quinolinedione and quinoxalinedione was showed in Figure 1 and Figure 2. The B ring in quinoxalinedione has more positive charge than quinolinedione even though there was one nitrogen difference between them. The electron distribution in heterocycles appeared to affect the reactivity.

The intercalation of compounds with human DNA was the insertion of a planar part of a molecule between two stacked base pairs.[12] The molecule must have 3-4 planar rings and the intercalation complex was parallel to the axis of the helix for an ideal intercalation.[13] We synthesized angular and planar heterocyclic compounds that had 3-4 rings and drew intercalation complexes of synthetic compounds by molecular modeling. As expected, the intercalation complex of planar heterocyclic compound **(9)** between GC/GC base pairs was parallel to the axis of the helix (Figure 3). However, DNA intercalation complex of angular heterocyclic compound **(6)** between GC/GC base pairs did not show the optimum intercalation (Figure 4). So, the planar heterocyclic compound was expected to have antitumor activity.

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The Molecular Mechanics Evaluation of the Stability of Bridgehead Olefins Containing Medium Rings

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The stability of bridgehead olefins containing 8 and 10 membered rings has been investigated by the MMX molecular mechanics calculation together with the GMMX conformational searching program. A number of 'hyperstable' bridgehead olefins, which have negative olefin strain values, have been found from the calculated values of strain energy and olefin strain for the series of *in-* and *out-* bicyclo[n.3.3]alk-1-ene and *in-* and *out-*bicyclo[n.4.4]alk-1-ene (n=1 to 8). For the bridgehead olefins with 'out' topology, hyperstable olefins were found in the systems having cyclononene or larger rings. For the bridgehead olefins with 'in' topology, hyperstable olefins were found in the systems having cyclodecene or larger rings.

Introduction

Double bonds at the bridgehead positions have been regarded as unstable and synthetically less accessible. This idea has been known as Bredt's rule, which states that the elimination to give a doule bond in a bridged bicyclic system always leads away from the bridgehead position.[1] Since the pioneering study by Bredt extensive research efforts have been made toward the synthesis, structural study, reactivity, and mechanistic study of strained bridgehead olefins. A number of review articles are now available.[2-4] Most research efforts on the bridgehad olefins, however, have