A Facile Synthesis of 5,14-Methano-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]quinoxalines by a 1,3-Dipolar Cycloaddition Reaction and an Intramolecular Alcoholysis

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The reaction of the hydrazones **5a-c** with 2-chloroacrylonitrile gave the 1,2-diazepino[3,4-*b*]quinoxaline hydrochlorides **6a-c**, which were converted into the 5,14-methano-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]-quinoxalines **7a-c**, respectively.

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In a previous paper [2], we reported that compound **1** was converted into the hydrazones **2a,b**, whose reaction with 2-chloroacrylonitrile resulted in the 1,3-dipolar cycloaddition reaction, isoxazolidine ring opening and then recyclization to give the 5-cyano-4-hydroxy-1,2-diazepino-[3,4-*b*]quinoxaline hydrochlorides **3a,b**, respectively, presumably *via* intermediates **A** and **B** (Chart 1). Moreover, the alcoholysis of **3a,b** afforded the 5-alkoxy-4-oxo-1,2-diazepino[3,4-*b*]quinoxalines **4a,b**, respectively. In the present investigation, we transformed compound **1** into the *o*-hydroxyphenylhydrazones **5a-c** (Scheme 1) so as to synthesize new condensed quinoxalines by a 1,3-dipolar cycloaddition reaction and a subsequent intramolecular alcoholysis. Namely, the conversion of **5a-c** into the 3-(*o*-hydroxyphenyl)-1,2-diazepino[3,4-*b*]quinoxalines **6a-c** would lead to the synthesis of novel ring condensed quinoxalines **7a-c**, respectively. As was expected, the intramolecular alcoholysis of **6a-c** provided the 5,14-methano-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]quinoxalines **7a-c**, respectively. This paper describes a convenient synthesis of **7a-c**, which have a new ring system.

The reaction of compound **1** with 2-hydroxybenzaldehyde, 2-hydroxy-3-methoxybenzaldehyde and 5-bromo-2-hydroxybenzaldehyde gave 6-chloro-2-[2-(2-hydroxybenzylidene)-1-methylhydrazino]quinoxaline 4-oxide **5a**, 6-chloro-2-[2-(2-hydroxy-3-methoxybenzylidene)-1-methylhydrazino]quinoxaline 4-oxide **5b** and 2-[2-(5-bromo-2-hydroxybenzylidene)-1-methylhydrazino]-6-chloroquinoxaline 4-oxide **5c**, respectively. The reaction of **5a-c** with 2-chloroacrylonitrile afforded 8-chloro-5-cyano-4-

Scheme 1

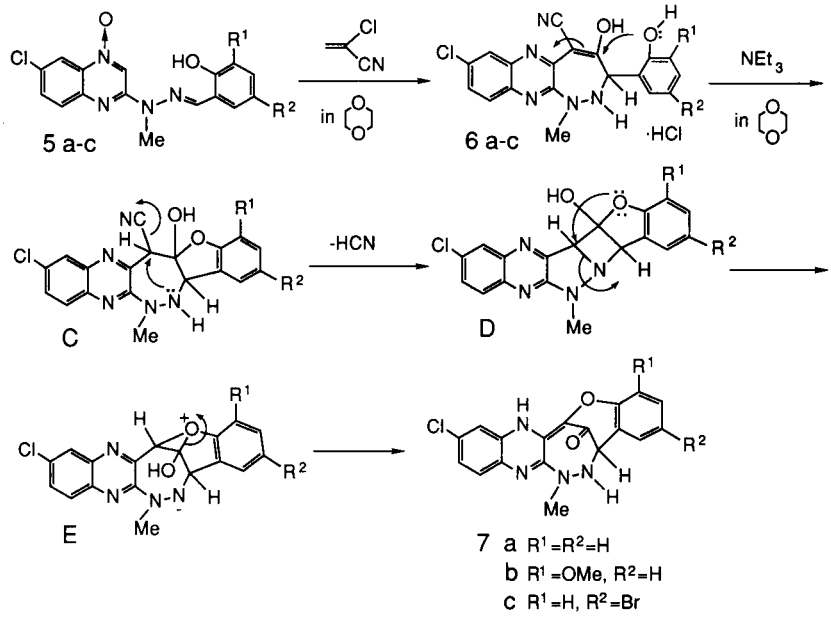
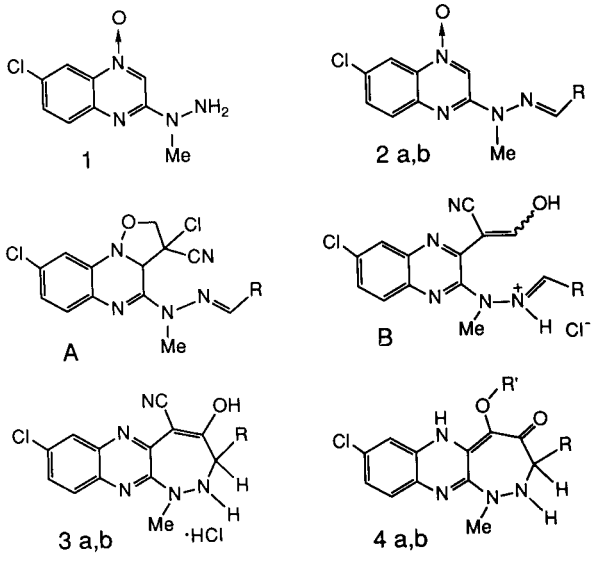


Chart 1



hydroxy-3-(2-hydroxyphenyl)-1-methyl-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline hydrochloride **6a**, 8-chloro-5-cyano-4-hydroxy-3-(2-hydroxy-3-methoxyphenyl)-1-methyl-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline hydrochloride **6b** and 3-(5-bromo-2-hydroxyphenyl)-8-chloro-5-cyano-4-hydroxy-1-methyl-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline hydrochloride **6c**, respectively. Refluxing of **6a-c** and triethylamine in dioxane provided 11-chloro-5,6,7,13-tetrahydro-5,14-methano-7-methyl-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]quinoxaline **7a**, 11-chloro-5,6,7,13-tetrahydro-5,14-methano-1-methoxy-7-methyl-16-oxo-1,5,6-benzoxadiazonino[3,4,-*b*]quinoxaline **7b** and 3-bromo-11-chloro-5,6,7,13-tetrahydro-5,14-methano-7-methyl-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]-quinoxaline **7c**, respectively, presumably *via* intermediates **C-E**.

The structural assignment of **5a-c**-**7a-c** was based on the analytical and spectral data. Especially, the nmr spectra of **7a,b** showed the C=O carbon signals at δ 162 ppm and the NOE between the N_{13}-H and C_{12}-H proton signals, between the C_4-H and C_5-H proton signals and among the C_5-H, N_6-H and N_7-Me proton signals (Chart 2, Table) [3]. The ir spectra of **7a-c** exhibited the C=O absorption band at 1650 cm^{-1}, which was a similar value to that of **4a,b** observed at 1640 cm^{-1} [2]. These ir and nmr spectral data eliminated the structure of **G** or **H** (Chart 3), which would be produced by the hydroxyl group migration *via* intermediates **D** and **F** shown in Chart 3. The ir spectra of **6a-c** showed the nitrile absorption band at 2200 cm^{-1}. The mass spectra of **6a-c** exhibited the molecular ion peaks in the FAB method, while the spectra lacked the molecular ion peaks in the DIEI method, showing the fragment ion peaks corresponding to **7a-c** [4].

Table

NOE Data for Compounds **7a,b**

Radiation	NOE	Compound 7a	7b
N_{13}-H	C_{12}-H	8.7	6.3 [a]
C_4-H	C_5-H	3.1	3.1
N_7-Me	C_5-H	6.2	3.9
	N_6-H	4.5	3.6

[a] Expressed in %.

Chart 2

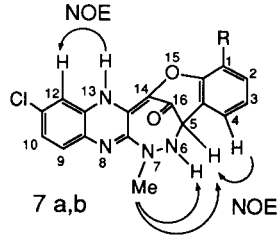
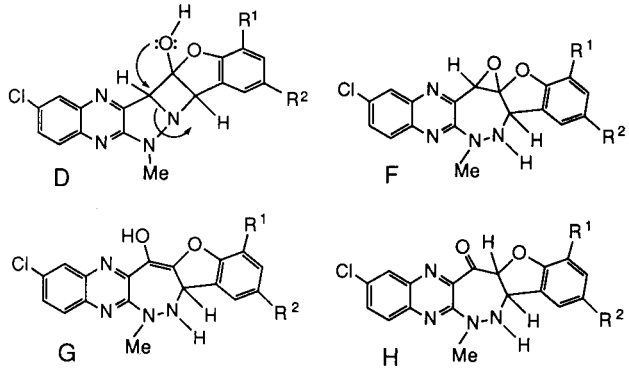


Chart 3



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-[2-(2-hydroxybenzilidene)-1-methylhydrazino]quinoxaline 4-Oxide **5a**, 6-Chloro-2-[2-(2-hydroxy-3-methoxybenzilidene)-1-methylhydrazino]quinoxaline 4-Oxide **5b** and 2-[2-(5-Bromo-2-hydroxybenzylidene)-1-methylhydrazino]-6-chloroquinoxaline 4-Oxide **5c**.

A solution of compound **1** (10 g, 44.5 mmoles) and 2-hydroxybenzaldehyde (8.15 g, 66.8 mmoles) in *N*,*N*-dimethylformamide

(150 ml) was refluxed in an oil bath for 2 hours to give a clear solution. The solution was cooled to room temperature to precipitate orange needles **5a**, which were triturated with ethanol and then collected by suction filtration. Washing with ethanol and then *n*-hexane gave an analytically pure sample (14.55 g, 100%).

Compound **5b** (orange needles, 15.8 g, 99%) was obtained by a similar manner to the above from the reaction of compound **1** (10 g, 44.5 mmoles) with 2-hydroxy-3-methoxybenzaldehyde (10.15 g, 66.75 mmoles) in *N,N*-dimethylformamide (150 ml).

Compound **5c** (yellow prisms, 17.55 g, 96%) was obtained in a similar manner to the above from the reaction of compound **1** (10 g, 44.5 mmoles) with 5-bromo-2-hydroxybenzaldehyde (13.43 g, 66.8 mmoles) in dioxane (200 ml).

Compound **5a** had mp 275-276°; ir: ν cm^{-1} 1595, 1565, 1525; ms: m/z 328 (M^+), 330 ($M^+ + 2$); pmr: 9.60 (br, 1H, OH), 8.90 (s, 1H, C_3-H), 8.26 (d, J = 2.0 Hz, 1H, C_5-H), 8.18 (s, 1H, hydrazone CH), 7.88 (dd, J = 7.5 Hz, J = 2.0 Hz, 1H, $C_{6'}$-H), 7.81 (d, J = 8.5 Hz, 1H, C_8-H), 7.77 (dd, J = 2.0, J = 8.5 Hz, 1H, C_7-H), 7.23 (ddd, J = 7.5 Hz, J = 7.5 Hz, J = 2.0 Hz, 1H, $C_{4'}$-H), 6.92 (d, J = 7.5 Hz, 1H, $C_{3'}$-H), 6.89 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H, $C_{5'}$-H), 3.69 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{13}ClN_4O_2$: C, 58.46; H, 3.98; Cl, 10.78; N, 17.04. Found: C, 58.33; H, 4.04; Cl, 10.93; N, 17.08.

Compound **5b** had mp 276-277°; ir: ν cm^{-1} 1595, 1565, 1520; ms: m/z 358 (M^+), 340 ($M^+ + 2$); pmr: 9.30 (br, 1H, OH), 8.89 (s, 1H, C_3-H), 8.28 (d, J = 2.5 Hz, 1H, C_5-H), 8.23 (s, 1H, hydrazone CH), 7.83 (d, J = 9.0 Hz, 1H, C_8-H), 7.78 (dd, J = 2.5 Hz, J = 9.0 Hz, 1H, C_7-H), 7.47 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, $C_{6'}$-H), 7.00 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, $C_{4'}$-H), 6.87 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, $C_{5'}$-H), 3.84 (s, 3H, OCH_3), 3.70 (s, 3H, NCH_3).

Anal. Calcd. for $C_{17}H_{15}ClN_4O_3$: C, 56.91; H, 4.21; Cl, 9.88; N, 15.62. Found: C, 56.68; H, 4.14; Cl, 9.86; N, 15.53.

Compound **5c** had mp 300-301°; ir: ν cm^{-1} 1590, 1565, 1520; ms: m/z 408 (M^+), 410 ($M^+ + 2$); pmr: 10.60 (br, 1H, OH), 8.96 (s, 1H, C_3-H), 8.28 (d, J = 2.1 Hz, 1H, C_5-H), 8.11 (s, 1H, hydrazone CH), 7.98 (d, J = 2.5 Hz, 1H, $C_{6'}$-H), 7.88 (d, J = 9.0 Hz, 1H, C_8-H), 7.78 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H, C_7-H), 7.35 (dd, J = 2.5 Hz, J = 8.5 Hz, 1H, $C_{4'}$-H), 6.89 (d, J = 8.5 Hz, 1H, $C_{3'}$-H), 3.69 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{12}BrClN_4O_2$: C, 47.15; H, 2.95; N, 13.75. Found: C, 47.21; H, 2.89; N, 13.98.

8-Chloro-5-cyano-4-hydroxy-3-(2-hydroxyphenyl)-1-methyl-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline Hydrochloride **6a**, 8-Chloro-5-cyano-4-hydroxy-3-(2-hydroxy-3-methoxyphenyl)-1-methyl-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline Hydrochloride **6b** and 3-(5-Bromo-2-hydroxyphenyl)-8-chloro-5-cyano-4-hydroxy-1-methyl-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline Hydrochloride **6c**.

A suspension of **5a** (10 g, 30.4 mmoles) and 2-chloroacrylonitrile (10.64 g, 121.6 mmoles) in dioxane (500 ml) was refluxed in an oil bath for 3 hours to give a clear solution. The solution was allowed to stand overnight at room temperature to precipitate yellow needles **6a**, which were collected by suction filtration and washed with dioxane and then *n*-hexane (9.69 g, 76%).

Compound **6b** (yellow needles, 11.44 g, 92%) and **6c** (yellow needles, 5.75 g, 48%) were obtained by a similar manner to the above from the reaction of **5b** (10 g, 28.0 mmoles) and **5c** (10 g, 24.6 mmoles) with 2-chloroacrylonitrile [(9.80 g, 112.0 mmoles), 5.38 g, 61.5 mmoles)] in dioxane (500 ml), respectively.

Compound **6a** had mp 228-229°; ir: ν cm^{-1} 3460, 3140, 3060, 3020, 2220, 1610, 1600, 1585, 1570; ms (FAB method): m/z 379 (M^+).

Compound **6b** had mp 185-186°; ir: ν cm^{-1} 3140, 3080, 3020, 2940, 2840, 2220, 1610, 1590, 1570; ms (FAB method): m/z 410 (M^+).

Compound **6c** had mp 168-169°; ir: ν cm^{-1} 3120, 3010, 2960, 2900, 2840, 2220, 1610, 1580, 1565; ms (FAB method): m/z 457 (M^+).

11-Chloro-5,6,7,13-tetrahydro-5,14-methano-7-methyl-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]quinoxaline **7a**.

A solution of **6a** (5 g, 12.0 mmoles) and triethylamine (1.82 g, 18.0 mmoles) in dioxane (200 ml) was refluxed in an oil bath for 2 hours to precipitate colorless needles of triethylamine hydrochloride. After the colorless needles were filtered off, the filtrate was evaporated *in vacuo* to give brown crystals **7a**, which were triturated with ethanol/water (1:1) and then collected by suction filtration (3.17 g). Evaporation of the filtrate afforded brown crystals **7a** (0.49 g), total yield, 3.66 g (86%). Recrystallization from dioxane/ethanol/water gave brick red needles, mp 255-256°; ir: ν cm^{-1} 1650, 1590, 1530; ms: m/z 352 (M^+), 354 ($M^+ + 2$); pmr: 11.88 (s, 1H, N_{13}-H), 7.81 (d, J = 2.0 Hz, 1H, C_{12}-H), 7.59 (d, J = 7.5 Hz, 1H, C_4-H), 7.39 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H, C_2-H or C_3-H), 7.34 (d, J = 8.5 Hz, 1H, C_9-H), 7.21 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H, C_3-H or C_2-H), 7.16 (dd, J = 2.0 Hz, J = 8.5 Hz, 1H, C_{10}-H), 7.12 (d, J = 7.5 Hz, 1H, C_1-H), 5.80 (d, J = 12.5 Hz, 1H, N_6-H), 5.28 (d, J = 12.5 Hz, 1H, C_5-H), 3.30 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; Cl, 10.05; N, 15.88. Found: C, 61.06; H, 3.77; Cl, 10.06; N, 15.72.

11-Chloro-5,6,7,13-tetrahydro-5,14-methano-1-methoxy-7-methyl-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]quinoxaline **7b**.

A solution of **6b** (5 g, 11.2 mmoles) and triethylamine (1.70 g, 16.8 mmoles) in dioxane (200 ml) was refluxed in an oil bath for 2 hours to precipitate colorless needles of triethylamine hydrochloride. After the colorless needles were filtered off, the filtrate was evaporated *in vacuo* to give brown crystals **7b**, which were triturated with ethanol/water (1:1) and then collected by suction filtration (3.64 g, 85%). Recrystallization from dioxane/ethanol/water afforded brick red needles, mp 263-264°; ir: ν cm^{-1} 1650, 1590, 1580, 1525; ms: m/z 382 (M^+), 384 ($M^+ + 2$); pmr: 11.87 (s, 1H, N_{13}-H), 7.82 (d, J = 2.5 Hz, 1H, C_{12}-H), 7.34 (d, J = 8.5 Hz, 1H, C_9-H), 7.16 (dd, J = 2.5 Hz, J = 8.5 Hz, 1H, C_{10}-H), 7.16-7.06 (m, 3H, C_2-H, C_3-H, C_4-H), 5.77 (d, J = 12.5 Hz, 1H, N_6-H), 5.27 (d, J = 12.5 Hz, 1H, C_5-H), 3.84 (s, 3H, OCH_3), 3.30 (s, 3H, NCH_3). The C_2-H and C_4-H proton signals were found to appear at δ 7.09 and 7.15 ppm, respectively, by the NOE measurement.

Anal. Calcd. for $C_{19}H_{15}ClN_4O_3$: C, 59.61; H, 3.95; Cl, 9.26; N, 14.64. Found: C, 59.57; H, 3.69; Cl, 9.21; N, 14.69.

3-Bromo-11-chloro-5,6,7,13-tetrahydro-5,14-methano-7-methyl-16-oxo-1,5,6-benzoxadiazonino[3,4-*b*]quinoxaline **7c**.

A solution of **6c** (5 g, 10.1 mmoles) and triethylamine (1.54 g, 15.2 mmoles) in dioxane (200 ml) was refluxed in an oil bath for 2 hours to precipitate a mixture of brick red needles **7c** and colorless needles (triethylamine hydrochloride), whose collection by suction filtration and then washing with ethanol/water (1:1) gave an analytically pure sample of **7c** (2.76 g). Evaporation of the filtrate *in vacuo* afforded crystals, whose trituration with diox-

ane/ethanol/water provided **7c** (0.40 g), total yield, 3.16 g (73%). Compound **7c** had mp 285-286°; ir: ν cm^{-1} 1650, 1590, 1565, 1535; ms: m/z 430 (M^+), 432 ($M^+ + 2$); pmr: 11.88 (br, 1H, N_{13}-H), 7.84 (d, J = 2.5 Hz, 1H, C_{12}-H), 7.66 (dd, J = 2.5 Hz, J = 1.0 Hz, 1H, C_4-H), 7.56 (ddd, J = 8.5 Hz, J = 2.5 Hz, J = 1.0 Hz, 1H, C_2-H), 7.36 (d, J = 8.5 Hz, 1H, C_9-H), 7.18 (dd, J = 2.5 Hz, J = 8.5 Hz, 1H, C_{10}-H), 7.12 (d, J = 8.5 Hz, 1H, C_1-H), 5.87 (d, J = 12.5 Hz, 1H, N_6-H), 5.31 (d, J = 12.5 Hz, 1H, C_5-H), 3.31 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{12}BrClN_4O_2$: C, 50.08; H, 2.80; N, 12.98. Found: C, 50.27; H, 2.79; N, 13.24.

REFERENCES AND NOTES

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[2] H. S. Kim, Y. Kurasawa, C. Yoshii, M. Masuyama, A. Takada and Y. Okamoto, *J. Heterocyclic Chem.*, **27**, 819 (1990).

[3] Since compound **7c** was insoluble in an ordinary solvent, its ^{13}C-nmr and NOE data were not obtained. Accordingly, only an ^1H-nmr spectral data was shown in the experimental part.

[4] The purification of the hydrochlorides **6a-c** was very difficult, since treatment of **6a-c** with a base spontaneously changed into **7a-c**, respectively. Accordingly, **6a-c** were checked by the ir and mass spectral data.