A Convenient Synthesis of 1,2-Diazepino[3,4-*b*]-quinoxalines *via* a 1,3-Dipolar Cycloaddition Reaction and Their Tautomeric Structure in a Solution [1]

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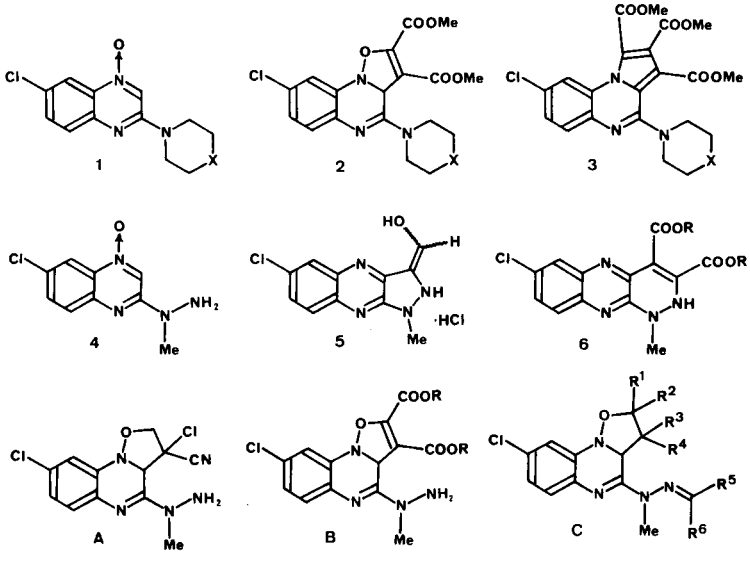
Received April 30, 1990

The reaction of the quinoxaline 4-oxides **7a,b** with 2-chloroacrylonitrile resulted in the 1,3-dipolar cycloaddition reaction and further alteration to give the 4-hydroxy-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxalines **8a,b** and **9a,b**, respectively, which were converted into the 4-oxo-2,3,4,6-tetrahydro-1*H*-1,2-diazepino[3,4-*b*]-quinoxalines **10a,b-12a,b**, respectively. The 2,3-dihydro-4-hydroxy form of **9a,b** and the 2,3,4,6-tetrahydro-4-oxo form of **10a,b-12a,b** were assigned by means of the NOE and ^{13}C-nmr spectral data.

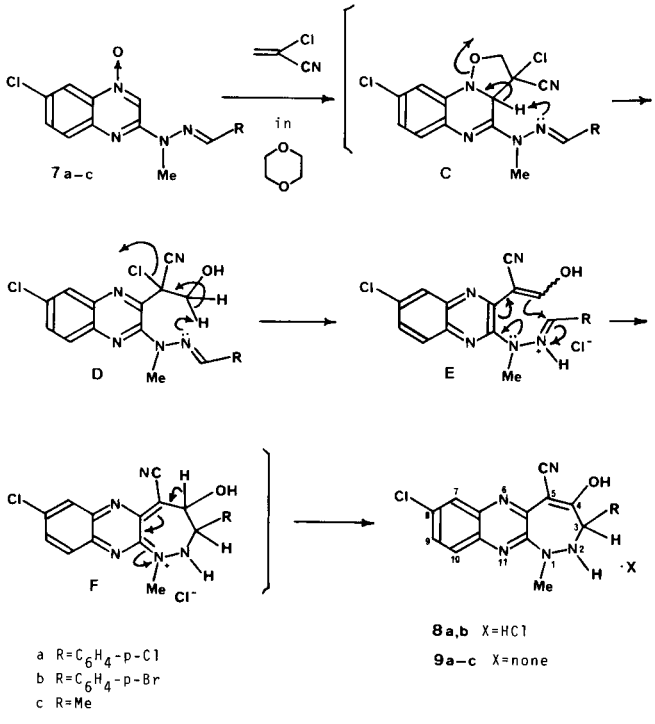
J. Heterocyclic Chem., **27**, 2197 (1990).

In a previous paper [3], we reported that the reaction of the quinoxaline 4-oxides **1** with an equimolar or 2-fold molar amount of dimethyl acetylenedicarboxylate selectively afforded the isoxazolo[2,3-*a*]quinoxalines **2** or pyrrolo[1,2-*a*]quinoxalines **3**, respectively (Chart 1). Thereafter, we found that the reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **4** with 2-chloroacrylonitrile or dialkoxy acetylenedicarboxylates provided the pyrazolo-[3,4-*b*]quinoxaline **5** or pyridazino[3,4-*b*]quinoxalines **6** presumably *via* an intermediate **A** or **B**, respectively [4]. The presence of the C_2-methylhydrazino group in **4** conveniently produced the linear type of condensed quinoxalines **5** and **6**. In order to extend the scope of the above reactions, we further modified the C_2-methylhydrazino function in the present investigation. Namely, if the methylhydrazino group of an intermediate **A** or **B** is blocked beforehand with an aldehyde or ketone, an intermediate such as **C** would be formed in the above reactions. Successively, an intermediate **C** would be converted into a different type of product from **5** or **6**. As might be expected, an intermediate **C** underwent an interesting alteration involving the ring opening and then recyclization to change into the 1,2-diazepino[3,4-*b*]quinoxalines **8** (Scheme 1). This paper describes a facile synthesis of the 1,2-diazepino[3,4-*b*]quinoxalines **8-12** *via* the 1,3-dipolar cycloaddition reaction and the tautomeric structures of **9-12** in a solution (Scheme 1, 2 and 4).

Chart 1



Scheme 1



a R=C_6H_4-p-Cl
b R=C_6H_4-p-Br
c R=Me

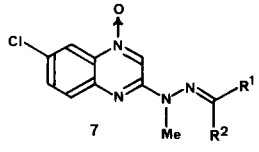
8a,b X=HCl
9a–c X=none

The reaction of **4** with *p*-chlorobenzaldehyde, *p*-bromobenzaldehyde, acetaldehyde and acetone gave the hydrazones **7a-d**, respectively (Chart 2). Among these hydrazones, **7a-c** gave the favorable results for the synthesis of the 1,2-diazepino[3,4-*b*]quinoxalines.

Table 1
Yield of Compounds **8a,b** and **9a,b**

Method	Yield% Hydrochloride	Free base
1	**8a** (79)	**9a** (12)
	8b (71)	**9b** (24)
2	—	**9a** (99)
	8b (16)	**9b** (78)

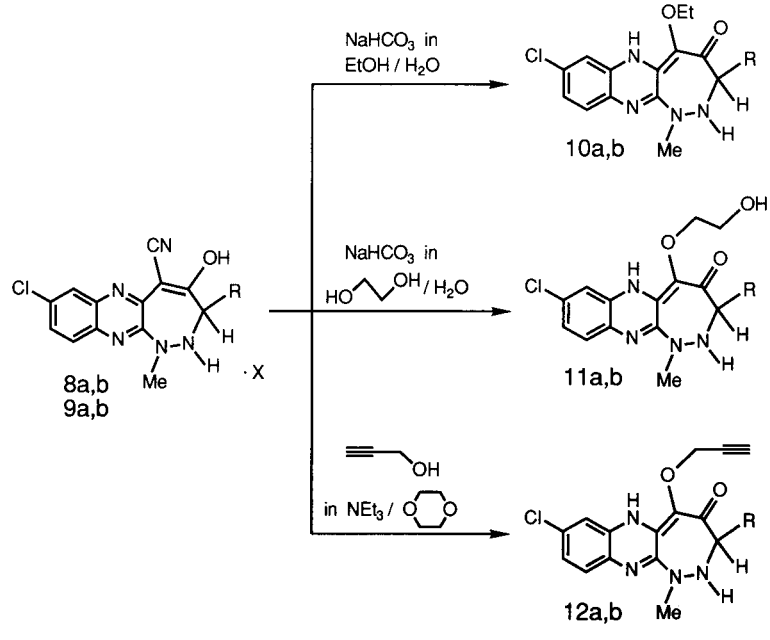
Chart 2



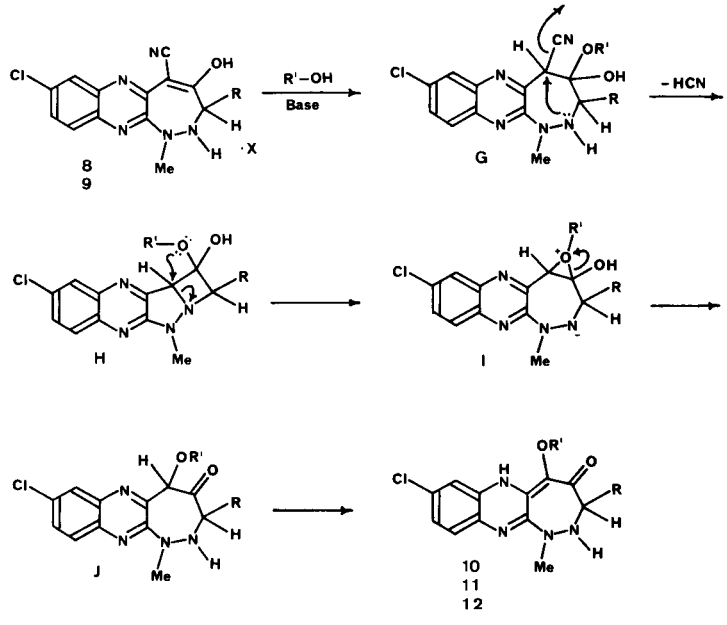
a R^1=C_6H_4-p-Cl, R^2=H
b R^1=C_6H_4-p-Br, R^2=H
c R^1=Me, R^2=H
d R^1=R^2=Me

The reaction of **7a-c** with 2-chloroacrylonitrile under reflux in dioxane afforded the 5-cyano-4-hydroxy-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline hydrochlorides **8a,b** and/or the free bases **9a-c**, respectively, presumably *via* intermediates **C-F** (Scheme 1). When the above reaction mixture was allowed to stand overnight, the yields of the hydrochlorides **8a,b** were predominant (Method 1) (Table 1). To the contrary, when the solvent was evaporated immediately after the reaction, the free bases **9a,b** were the main product (Method 2). Compound **9c** was obtained by Method 2.

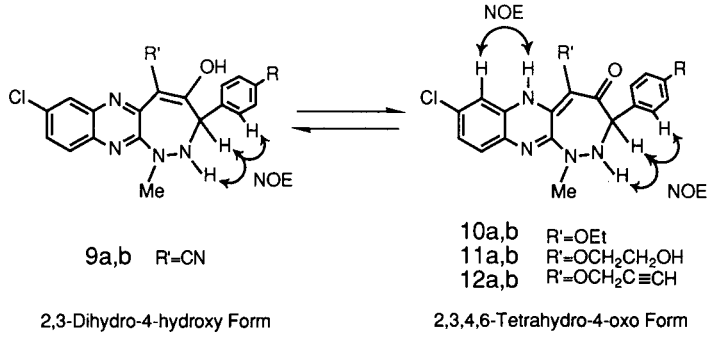
Scheme 2



Scheme 3



Scheme 4



The C_5-cyano group of **8a,b** and **9a,b** was easily replaced with alkoxyl group in the presence of a base (Scheme 2). Refluxing of **8a,b** and sodium bicarbonate in water/ethanol or water/ethylene glycol resulted in alcoholysis to provide the 5-ethoxy-4-oxo-2,3,4,6-tetrahydro-1*H*-1,2-diazepino[3,4-*b*]quinoxalines **10a,b** or 5-(2-hydroxyethoxy)-4-oxo-2,3,4,6-tetrahydro-1*H*-1,2-diazepino[3,4-*b*]quinoxalines **11a,b**, respectively, and refluxing of **9a,b** and propargyl alcohol in triethylamine/dioxane furnished the 5-propargyloxy-4-oxo-2,3,4,6-tetrahydro-1*H*-1,2-diazepino-[3,4-*b*]quinoxalines **12a,b**, respectively. The above alcoholysis might proceed *via* intermediates **G-J** [5-7] (Scheme 3).

Table 2

NOE Data for Compounds **9-12**

		Compound							
Radiation	NOE	**9a**	**9b**	**10a**	**10b**	**11a**	**11b**	**12a**	**12b**
N_2-H	C_3-H	3.5	10.5	9.7	8.3	10.0	8.5	11.0	11.7 [a]
C_3-H	N_2-H	—	3.8	7.2	5.3	6.0	5.3	6.5	6.9
	$C_{2'}$-H	7.0	6.0	6.4	7.4	6.7	6.8	7.7	8.3
C_2-H	C_3-H	—	3.0	4.8	3.2	5.0	2.3	—	—
N_6-H	C_7-H	—	—	10.1	11.1	11.0	10.8	12.3	11.7
C_7-H	N_6-H	—	—	8.9	9.1	4.0	3.8	3.9	4.1

[a] Expressed in %.

The structural assignment of **7-12** was based on the analytical and spectral data. The 2,3,4,6-tetrahydro-4-oxo form of **10a,b-12a,b** was ascertained by the NOE measurement between the N_6-H and C_7-H proton signals and among the N_2-H, C_3-H and C_2-H proton signals (Table 2) as well as the observation of the carbonyl carbon signals at δ 168.52-166.47 ppm (Table 3), while the 2,3-dihydro-4-hydroxy form of **9a,b** was supported by the NOE measurement among the N_2-H, C_3-H and C_2-H proton signals (Scheme 4). The nmr spectra of **9a,b** showed no signal due to the carbonyl carbon and no NOE due to the radiation at the C_7-H proton signal. These data eliminated the 2,3,4,6-tetrahydro-4-oxo form for **9a,b**. Thus, **9a,b** were found to exist as the 2,3-dihydro-4-hydroxy form, while **10a,b-12a,b** were predominant as the 2,3,4,6-tetrahydro-4-oxo form at least in a solution.

Compound **9c** was also assigned as the 2,3-dihydro-4-hydroxy form, since the ^{1}H- and ^{13}C-nmr spectra of **9c** showed the C_4-OH proton signal at δ 14.36 ppm and exhibited no C=O carbon signal near δ 167 ppm, respectively. Moreover, the C_{5a}-C_{11a} carbon signals of **9c** appeared in a similar magnetic field to those of **9a,b**, while the chemical shifts of the C_3-C_5 carbon signals in **9c** were slightly different from those in **9a,b** because of the difference in the C_3-substituent (Table 4).

The nmr spectra of **12a,b** showed two kinds of acetylenic carbon signals at δ 78.94 and 77.39 ppm (Table 3), but not allene carbon signals, denying the isomerization of the acetylenes **12a,b** into the allenes **K** (Chart 3).

Table 3

^{13}C-NMR Spectral Data for Compounds **10-12**

Carbon	Compound 10a	10b	11a	11b	12a	12b
C_3	55.97	56.03	54.92	54.98	54.86	54.93
C_4=0	168.52	168.52	167.35	167.35	166.48	166.47
C_5	92.34	92.25	92.78	92.71	91.44	91.34
C_{11a}	149.88	149.86	150.34	150.34	150.25	150.25
N_1-Me	38.26	38.26	38.27	38.27	38.32	38.32
HC≡-	—	—	—	—	77.39	77.39
≡C-	—	—	—	—	78.94	78.94

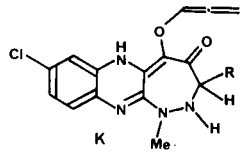
Table 4

^{13}C-NMR Spectral Data for Compounds **9a-c** [a]

Carbon	Compound 9a	9b	9c
C_3	56.48	56.53	50.06
C_4	155.02	155.14	152.60
C_5	105.46	105.31	110.09
C_{5a}	126.42	126.37	126.95
C_{6a}	137.36	137.34	137.13
C_7	118.28	118.25	118.57
C_8	131.88	131.89	131.57
C_9	128.87	128.88	128.70
C_{10}	127.78	127.70	127.62
C_{10a}	136.70	136.68	136.80
C_{11a}	148.95	148.93	148.84
N_1-Me	38.39	38.41	38.64
CN	113.30	113.29	113.41

[a] Carbon signal assignment was based on the one bond and long range ^{1}H-^{13}C COSY spectral data.

Chart 3



In the tautomer change of the 2,3-dihydro-4-hydroxy form into the 2,3,4,6-tetrahydro-4-oxo form, the C_5 as well as C_4 carbon signals were eminently varied, while the C_3, N_1-Me and C_{11a} carbon signals were not altered considerably (Table 3, 4).

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 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-(*p*-chlorobenzylidene)-1-methylhydrazino]quinoxaline 4-Oxide **7a** and 2-[2-(*p*-Bromobenzylidene)-1-methylhydrazino]-6-chloroquinoxaline 4-Oxide **7b**.

A solution of **4** (10 g, 44.5 mmoles) and *p*-chlorobenzaldehyde (7.51 g, 53.5 mmoles) or *p*-bromobenzaldehyde (9.88 g, 53.5 mmoles) in *N,N*-dimethylformamide (150 ml) was refluxed in an oil bath for 1 hour to precipitate yellow needles **7a** or **7b**, respectively. After cooling to room temperature, an addition of ethanol (100 ml) to the above reaction mixture and then collection of the yellow needles by suction filtration provided an analytically pure sample of **7a** (15.30 g, 99%) or **7b** (17.41 g, 100%).

Compound **7a** had mp above 320°; ir: ν cm^{-1} 1582, 1570, 1525; ms: m/z 346 (M^+), 348 (M^++2); pmr (deuteriotrifluoroacetic acid): 8.97 (s, 1H, C_3-H), 8.27 (s, 1H, C_5-H), 8.19 (s, 1H, hydrazone CH), 7.71 (s, 2H, C_7-H and C_8-H), 7.56 (d, J = 8.5 Hz, 2H, aromatic), 7.24 (d, J = 8.5 Hz, 2H, aromatic), 3.63 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{12}Cl_2N_4O$: C, 55.35; H, 3.48; Cl, 20.42; N, 16.14. Found: C, 55.17; H, 3.46; Cl, 20.14; N, 16.22.

Compound **7b** had mp above 320°; ir: ν cm^{-1} 1582, 1570, 1525; ms: m/z 390 (M^+), 392 (M^++2); pmr (deuteriotrifluoroacetic acid): 8.98 (s, 1H, C_3-H), 8.29 (s, 1H, C_5-H), 8.20 (s, 1H, hydrazone CH), 7.73 (s, 2H, C_7-H and C_8-H), 7.50 (d, J = 8.5 Hz, 2H, aromatic), 7.43 (d, J = 8.5 Hz, 2H, aromatic), 3.65 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{12}BrClN_4O$: C, 49.07; H, 3.09; N, 14.31. Found: C, 48.99; H, 3.07; N, 14.35.

6-Chloro-2-(2-ethylidene-1-methylhydrazino)quinoxaline 4-Oxide **7c**.

A solution of **4** (10 g) and acetaldehyde (20 ml) in *N,N*-dimethylformamide (180 ml) was heated at 120-140° in an oil bath for 2 hours. The solution was allowed to stand overnight at room temperature to precipitate yellow needles **7c**, which were collected by suction filtration. Trituration with hot ethanol gave an analytically pure sample of **7c** (10.93 g, 98%), mp 202-203°; ir: ν cm^{-1} 1620, 1600, 1570, 1525; ms: m/z 250 (M^+), 252 ($M^+ + 2$); pmr (deuteriotrifluoroacetic acid): 8.82 (s, 1H, C_3-H), 8.23 (s, 1H, C_5-H), 7.65 (s, 3H, C_7-H, C_8-H and hydrazone CH), 3.40 (s, 3H, N-CH_3), 1.98 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{11}ClN_4O$: C, 52.70; H, 4.42; Cl, 14.14; N, 22.35. Found: C, 52.41; H, 4.41; Cl, 14.07; N, 22.41.

6-Chloro-2-(2-isopropylidene-1-methylhydrazino)quinoxaline 4-Oxide **7d**.

A solution of **4** (10 g) in acetone (200 ml) was refluxed on a boiling water bath for 3 hours. The hot solution was immediately filtered, and the filtrate was allowed to stand at room temperature to precipitate analytically pure yellow prisms **7d**, which were collected by suction filtration (8.20 g). Evaporation of the filtrate *in vacuo* afforded additional yellow crystals **7d** (2.54 g) [total yield, 10.74 g (91%)]. Compound **7d** had mp 172-173°; ir: ν cm^{-1} 1620, 1600, 1570, 1530; ms: m/z 264 (M^+), 266 ($M^+ + 2$); pmr (deuteriochloroform): 8.40 (d, J = 2.5 Hz, 1H, C_5-H), 8.15 (s, 1H, C_3-H), 7.69 (d, J = 8.5 Hz, 1H, C_8-H), 7.55 (dd, J = 2.5 Hz, J = 8.5 Hz, 1H, C_7-H), 3.31 (s, 3H, N-CH_3), 2.17 (s, 3H, CH_3), 2.03 (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{13}ClN_4O$: C, 54.44; H, 4.95; Cl, 13.19; N, 21.16. Found: C, 54.26; H, 4.86; Cl, 13.48; N, 21.14.

8-Chloro-3-(*p*-chlorophenyl)-5-cyano-4-hydroxy-1-methyl-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline Hydrochloride **8a**, 3-(*p*-Bromophenyl)-8-chloro-5-cyano-4-hydroxy-1-methyl-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline Hydrochloride **8b** and Free Bases **9a,b**.

Method 1.

A suspension of **7a** (10 g, 28.8 mmoles) and 2-chloroacrylonitrile (10.08 g, 115.2 mmoles) in dioxane (600 ml) was refluxed in an oil bath for 4 hours to give a clear solution. The solution was allowed to stand overnight at room temperature to precipitate yellow needles **8a**, which were collected by suction filtration (9.87 g, 79%). Trituration with hot ethanol afforded an analytically pure sample of **8a**. Evaporation of the filtrate *in vacuo* provided brown crystals, whose trituration with hot ethanol/hexane and then collection by suction filtration gave the free base **9a** (1.32 g, 12%).

The hydrochloride **8b** (8.68 g, 71%) and the free base **9b** (2.70 g, 24%) were obtained by a similar manner to the above from the reaction of **7b** (10 g, 25.5 mmoles) with 2-chloroacrylonitrile (8.95 g, 102.0 mmoles) in dioxane (600 ml).

Method 2.

After the reaction of **7a** (10 g, 28.8 mmoles) with 2-chloroacrylonitrile (10.08 g, 115.2 mmoles) under reflux in dioxane (600 ml) for 4 hours, immediate evaporation of the solvent *in vacuo* gave brown crystals, which were taken up in hot dioxane. The hot dioxane solution was filtered to exclude a trace amount of impurities, and the filtrate was evaporated *in vacuo* to give brown crystals **9a**, which were triturated with hot ethanol/hexane and then collected by suction filtration (11.37 g, 99%).

After the reaction of **7b** (10 g, 25.5 mmoles) with 2-chloroacrylonitrile (8.95 g, 102.0 mmoles) under reflux in dioxane (600 ml) for 4 hours, immediate evaporation of the solvent *in vacuo* afforded brown crystals including the hydrochloride **8b** and free base **9b**. The free base **9b** was taken up in hot dioxane to separate the insoluble hydrochloride **8b** by suction filtration. The hydrochloride **8b** was washed with dioxane and then hexane to provide an analytically pure sample (1.96 g, 16%). The combined dioxane solution was evaporated *in vacuo* to give the free base **9b**, which were triturated with hot ethanol/hexane and then collected by suction filtration (8.79 g, 78%).

Compound **8a** had mp 216-217°; ir: ν cm^{-1} 3130, 3060, 3000, 2205, 1680, 1660; ms: m/z 397 (M^+), 399 ($M^+ + 2$).

Anal. Calcd. for $C_{19}H_{13}Cl_2N_5O \cdot HCl$: C, 52.50; H, 3.25; Cl, 24.47; N, 16.11. Found: C, 52.24; H, 3.28; Cl, 24.18; N, 15.83.

Compound **8b** had mp 214-215°; ir: ν cm^{-1} 3130, 3060, 3000, 2210, 1680, 1660; ms: m/z 441 (M^+), 443 ($M^+ + 2$).

Anal. Calcd. for $C_{19}H_{13}BrClN_5O \cdot HCl$: C, 47.63; H, 2.94; N, 14.62. Found: C, 47.87; H, 3.11; N, 14.54.

Compound **9a** was recrystallized from ethanol to give brown needles, mp 221-222°; ir: ν cm^{-1} 3200, 2210, 1590, 1550, 1520; ms: m/z 397 (M^+), 399 ($M^+ + 2$); pmr (deuteriochloroform): 14.55 (s, 1H, OH), 7.53 (d, J = 8.8 Hz, 1H, C_{10}-H), 7.45 (d, J = 2.1 Hz, 1H, C_7-H), 7.39 (dd, J = 8.8 Hz, J = 2.1 Hz, 1H, C_9-H), 7.31 (s, 4H, aromatic), 5.34 (d, J = 2.1 Hz, 1H, C_3-H), 4.70 (d, J = 2.1 Hz, 1H, N_2-H), 3.20 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{13}Cl_2N_5O$: C, 57.30; H, 3.29; Cl, 17.80; N, 17.59. Found: C, 57.14; H, 3.36; Cl, 17.59; N, 17.32.

Compound **9b** was recrystallized from ethanol to give brown needles, mp 225-226°; ir: ν cm^{-1} 3230, 2210, 1590, 1550, 1515; ms: m/z 441 (M^+), 443 ($M^+ + 2$); pmr (deuteriochloroform): 14.55 (s, 1H, OH), 7.53 (d, J = 9.0 Hz, 1H, C_{10}-H), 7.47 (d, J = 9.0 Hz, 2H, $C_{3'}$-H and $C_{5'}$-H), 7.45 (d, J = 2.4 Hz, 1H, C_7-H), 7.39 (dd, J = 9.0 Hz, J = 2.4 Hz, 1H, C_9-H), 7.25 (d, J = 9.0 Hz, 2H, $C_{2'}$-H and $C_{6'}$-H), 5.32 (d, J = 2.5 Hz, 1H, C_3-H), 4.70 (d, J = 2.5 Hz, 1H, N_2-H), 3.20 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{13}BrClN_5O$: C, 51.55; H, 2.96; N, 15.82. Found: C, 51.29; H, 3.03; N, 15.54.

8-Chloro-5-cyano-4-hydroxy-1,3-dimethyl-2,3-dihydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline **9c**.

A solution of **7c** (5 g, 20.0 mmoles) and 2-chloroacrylonitrile (4.38 g, 50.0 mmoles) in dioxane (250 ml) was refluxed in an oil bath for 1 hour to precipitate crystals. The solvent was immediately evaporated *in vacuo* to give brown crystals, which were dissolved in hot dioxane/hexane and then filtered. The filtrate was evaporated *in vacuo* to furnish brown crystals **9c** (3.01 g, 50%). Recrystallization from ethanol/hexane gave brown needles, mp 209-210°; ir: ν cm^{-1} 2220, 1590, 1550, 1520; ms: m/z 301 (M^+), 303 ($M^+ + 2$); pmr (deuteriochloroform): 14.36 (s, 1H, OH), 7.54 (dd, J = 8.0 Hz, J = 1.1 Hz, 1H, C_{10}-H), 7.39 (dd, J = 2.2 Hz, J = 1.1 Hz, 1H, C_7-H), 7.38 (dd, J = 8.0 Hz, J = 2.2 Hz, 1H, C_9-H), 4.40 (s, 1H, N_2-H), 4.33 (q, J = 7.0 Hz, 1H, C_3-H), 3.40 (s, 3H, N_1-CH_3), 1.48 (d, J = 7.0 Hz, 3H, C_3-CH_3).

Anal. Calcd. for $C_{14}H_{12}ClN_5O$: C, 55.73; H, 4.01; Cl, 11.75; N, 23.21. Found: C, 55.74; H, 4.12; Cl, 11.71; N, 22.95.

8-Chloro-3-(*p*-chlorophenyl)-5-ethoxy-1-methyl-4-oxo-2,3,4,6-tetrahydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline **10a** and 3-(*p*-Bromophenyl)-8-chloro-5-ethoxy-1-methyl-4-oxo-2,3,4,6-tetrahydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline **10b**.

A solution of **8a** (5 g, 11.50 mmoles) and sodium bicarbonate (1.16 g, 13.80 mmoles) in ethanol (450 ml)/water (50 ml) was refluxed on a boiling water bath for 2 hours to precipitate yellow needles **10a**, which were collected by suction filtration and then washed with ethanol/water to give an analytically pure sample (2.81 g, 59%). Evaporation of the filtrate *in vacuo* afforded yellow crystals, whose trituration with hot ethanol and then collection by suction filtration provided additional product **10a** (1.19 g, 25%) [total yield, 4.0 g (84%)].

Compound **10b** (3.97 g, 83%) was obtained by a similar manner to the above from the reaction of **8b** (5 g, 10.42 mmoles) with sodium bicarbonate (1.05 g, 12.50 mmoles) in ethanol (450 ml)/water (50 ml).

Compound **10a** had mp 229-230°; ir: ν cm^{-1} 3200, 2970, 1645, 1605, 1595; ms: m/z 416 (M^+), 418 (M^++2); pmr (deuteriochloroform): 11.74 (s, 1H, N_6-H), 7.26 (d, J = 8.5 Hz, 1H, C_{10}-H), 7.27-7.26 (m, 4H, aromatic), 7.02 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H, C_9-H), 6.99 (d, J = 2.1 Hz, 1H, C_7-H), 5.01 (s, 1H, C_3-H), 4.47 (s, 1H, N_2-H), 4.15 (q, J = 7.0 Hz, 2H, CH_2), 3.10 (s, 3H, CH_3), 1.16 (t, J = 7.0 Hz, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{18}Cl_2N_4O_2$: C, 57.57; H, 4.35; Cl, 17.00; N, 13.43. Found: C, 57.48; H, 4.24; Cl, 16.82; N, 13.24.

Compound **10b** had mp 234-235°; ir: ν cm^{-1} 3200, 2970, 2900, 1645, 1605, 1595; ms: m/z 460 (M^+), 462 (M^++2); pmr (deuteriochloroform): 11.75 (s, 1H, N_6-H), 7.41 (d, J = 8.5 Hz, 2H, $C_{3'}$-H and $C_{5'}$-H), 7.27 (d, J = 8.5 Hz, 1H, C_{10}-H), 7.22 (d, J = 8.5 Hz, 2H, $C_{2'}$-H and $C_{6'}$-H), 7.03 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H, C_9-H), 6.99 (d, J = 2.1 Hz, 1H, C_7-H), 5.00 (s, 1H, C_3-H), 4.46 (s, 1H, N_2-H), 4.15 (q, J = 7.0 Hz, 2H, CH_2), 3.10 (s, 3H, CH_3), 1.16 (t, J = 7.0 Hz, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{18}BrClN_4O_2$: C, 52.02; H, 3.93; N, 12.13. Found: C, 51.94; H, 3.83; N, 12.20.

8-Chloro-3-(*p*-chlorophenyl)-5-(2-hydroxyethoxy)-1-methyl-4-oxo-2,3,4,6-tetrahydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline **11a** and 3-(*p*-Bromophenyl)-8-chloro-5-(2-hydroxyethoxy)-1-methyl-4-oxo-2,3,4,6-tetrahydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline **11b**.

A suspension of **8a** (5 g, 11.50 mmoles) and sodium bicarbonate (1.16 g, 13.80 mmoles) in ethylene glycol (170 ml)/water (30 ml) was heated on a boiling water bath for 2 hours to precipitate yellow crystals **11a**, which were collected by suction filtration (3.77 g, 76%).

Compound **11b** (3.94 g, 79%) was obtained by a similar manner to the above from the reaction of **8b** (5 g, 10.42 mmoles) with sodium bicarbonate (1.05 g, 12.50 mmoles) in ethylene glycol (170 ml)/water (30 ml).

Compound **11a** was recrystallized from chloroform to give yellow needles, mp 219-220°; ir: ν cm^{-1} 3190, 2930, 1638, 1605, 1595; ms: m/z 432 (M^+), 434 (M^++2); pmr (deuteriodimethyl sulfoxide): 11.50 (s, 1H, N_6-H), 7.54 (d, J = 2.1 Hz, 1H, C_7-H), 7.34 (s, 4H, aromatic), 7.21 (d, J = 8.5 Hz, 1H, C_{10}-H), 7.03 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H, C_9-H), 6.05 (d, J = 3.0 Hz, N_2-H), 5.00 (d, J = 3.0 Hz, 1H, C_3-H), 4.83 (t, J = 5.0 Hz, 1H, OH), 4.18 (dt, J = 10.0 Hz, J = 5.0 Hz, 1H, ethylene $C_{1'}$-H), 4.01 (dt, J = 10.0 Hz, J = 5.0 Hz, 1H, ethylene $C_{1'}$-H), 3.53 (dt, J = 5.0 Hz, J = 5.0 Hz, 2H, ethylene $C_{2'}$-H), 2.99 (s, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{18}Cl_2N_4O_3 \cdot \frac{1}{2}H_2O$: C, 54.31; H, 4.33; Cl, 16.03; N, 12.67. Found: C, 54.40; H, 4.09; Cl, 16.28; N, 12.75.

Compound **11b** was recrystallized from chloroform to give yellow needles, mp 217-218°; ir: ν cm^{-1} 3195, 2920, 1638, 1605, 1595; ms: m/z 476 (M^+), 478 (M^++2); pmr (deuteriodimethyl sulfoxide): 11.50 (s, 1H, N_6-H), 7.54 (d, J = 2.1 Hz, 1H, C_7-H), 7.47 (d, J = 8.5 Hz, 2H, aromatic $C_{3'}$-H and $C_{5'}$-H), 7.28 (d, 8.5 Hz, 2H, aromatic $C_{2'}$-H and $C_{6'}$-H), 7.21 (d, J = 8.5 Hz, 1H, C_{10}-H), 7.03 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H, C_9-H), 6.05 (d, J = 2.8 Hz, 1H, N_2-H), 4.98 (d, J = 2.8 Hz, 1H, C_3-H), 4.83 (t, J = 5.0 Hz, 1H, OH), 4.18 (dt, J = 10.0 Hz, J = 5.0 Hz, 1H, ethylene $C_{1'}$-H), 4.01 (dt, J = 10.0 Hz, J = 5.0 Hz, 1H, ethylene $C_{1'}$-H), 3.53 (dt, J = 5.0 Hz, J = 5.0 Hz, 2H, ethylene $C_{2'}$-H), 2.99 (s, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{18}BrClN_4O_3 \cdot \frac{1}{2}H_2O$: C, 49.35; H, 3.93; N, 11.51. Found: C, 49.19; H, 3.64; N, 11.50.

8-Chloro-3-(*p*-chlorophenyl)-1-methyl-5-propargyloxy-4-oxo-2,3,-4,6-tetrahydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline **12a** and 3-(*p*-Bromophenyl)-8-chloro-1-methyl-5-propargyloxy-4-oxo-2,3,-4,6-tetrahydro-1*H*-1,2-diazepino[3,4-*b*]quinoxaline **12b**.

A solution of **9a** (5 g) and propargyl alcohol (10 ml) in triethylamine (2 ml)/dioxane (140 ml) was heated on a boiling water bath for 2 hours. Evaporation of the solvent *in vacuo* afforded yellow needles **12a**, which were triturated with ethanol/hexane and then collected by suction filtration (3.97 g). Evaporation of the filtrate *in vacuo* provided additional yellow crystals **12a**, which were triturated with ethanol/hexane and then collected by suction filtration (0.4 g) [total yield, 4.37 g (82%)].

Compound **12b** (5.33 g, 72%) was obtained by a similar manner to the above from the reaction of **9b** (5 g) with propargyl alcohol (10 ml) in triethylamine (2 ml)/dioxane (140 ml).

Compound **12a** was recrystallized from dioxane/ethanol to give yellow cottony needles, mp 223-224°; ir: ν cm^{-1} 3270, 3210, 2950, 2900, 2840, 2100, 1635, 1600; ms: m/z 426 (M^+), 428 (M^++2); pmr (deuteriodimethyl sulfoxide): 11.62 (s, 1H, N_6-H), 7.68 (d, J = 2.1 Hz, 1H, C_7-H), 7.34 (s, 4H, aromatic), 7.23 (d, J = 8.5 Hz, 1H, C_{10}-H), 7.06 (dd, J = 2.1 Hz, J = 8.5 Hz, 1H, C_9-H), 6.09 (d, J = 3.0 Hz, 1H, N_2-H), 4.96 (d, J = 3.0 Hz, 1H, C_3-H), 4.78 (dd, J = 16.0 Hz, J = 2.5 Hz, 1H, methylene CH), 4.70 (dd, J = 16.0 Hz, J = 2.5 Hz, 1H, methylene CH), 3.48 (dd, J = 2.5 Hz, J = 2.5 Hz, 1H, acetylene CH), 2.97 (s, 3H, CH_3).

Anal. Calcd. for $C_{21}H_{16}Cl_2N_4O_2$: C, 59.03; H, 3.77; Cl, 16.59; N, 13.11. Found: C, 59.21; H, 3.61; Cl, 16.36; N, 13.31.

Compound **12b** was recrystallized from dioxane/ethanol to give yellow cottony needles, mp 221-222°; ir: ν cm^{-1} 3290, 3210, 2950, 2900, 2840, 2100, 1635, 1600; ms: m/z 470 (M^+), 472 (M^++2); pmr (deuteriodimethyl sulfoxide): 11.62 (s, 1H, N_6-H), 7.69 (d, J = 2.1 Hz, 1H, C_7-H), 7.47 (d, J = 8.5 Hz, 2H, $C_{3'}$-H and $C_{5'}$-H), 7.27 (d, J = 8.5 Hz, 2H, $C_{2'}$-H and $C_{6'}$-H), 7.23 (d, J = 8.5 Hz, 1H, C_{10}-H), 7.07 (dd, J = 2.1 Hz, J = 8.5 Hz, 1H, C_9-H), 6.09 (d, J = 3.0 Hz, 1H, N_2-H), 4.94 (d, J = 3.0 Hz, 1H, C_3-H), 4.78 (dd, J = 16.0 Hz, J = 2.5 Hz, 1H, methylene CH), 4.70 (dd, J = 16.0 Hz, J = 2.5 Hz, 1H, methylene CH), 3.48 (dd, J = 2.5 Hz, J = 2.5 Hz, 1H, acetylene CH), 2.97 (s, 3H, CH_3).

Anal. Calcd. for $C_{21}H_{16}BrClN_4O_2$: C, 53.47; H, 3.42; N, 11.88. Found: C, 53.41; H, 3.56; N, 11.74.

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