Synthesis of Novel Quinoxalines by Ring Transformation of 3-Quinoxalinyl-1,5-benzodiazepine [1]

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Ring transformation of the 3-quinoxalinyl-1,5-benzodiazepine (**2**) gave 3-(benzimidazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline hydrochloride (**4a**), whose treatment with 5% sodium hydroxide provided the free base **5a**, while refluxing of the 3'-chloro-1-formyl derivative **3** in acetic acid and in 10% hydrochloric acid/acetic acid afforded 3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-1-formyl-2-oxo-3*H*-1,5-benzodiazepine hydrochloride (**7**) and 3-methyl-2-oxo-1,2-dihydroquinoxaline (**6**), respectively. Compounds **4a** and **5a** were converted into 3-(α-hydroxyiminobenzimidazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxaline (**8**) and 3-(benzimidazol-2-ylcarbonyl)-2-oxo-1,2-dihydroquinoxaline (**10**), respectively, which were further transformed into 3-(benzimidazol-2-yl)isoxazolo[4,5-*b*]quinoxaline (**9**) and 12-(benzimidazol-2-yl)-6*H*-quinoxalino[2,3-*b*][1,5]benzodiazepine (**11**), respectively.

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In previous papers [2], we reported a ring transformation of 3-(*N,N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride (**1**) into 3-(3-oxo-1,2,3,4-tetrahydroquinoxalin-2-ylidene)-1,2-dihydro-2-oxo-3*H*-1,5-benzodiazepine hydrochloride (**2a**) or its tautomer **2b**, which was further converted into 3-(3-chloroquinoxalin-2-yl)-1,2-dihydro-1-formyl-2-oxo-3*H*-1,5-benzodiazepine (**3**) (Chart 1). Some 1,5-benzodiazepines have been transformed into benzimidazoles under acidic conditions [3], and hence the 1,5-benzodiazepine rings of **2** and **3** are expected to be converted into the benzimidazole rings. In fact, **2** was transformed into 3-(benzimidazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline hydrochloride (**4a**), although **3** was changed into 3-methyl-2-oxo-1,2-dihydroquinoxaline (**6**). Moreover, the novel benzimidazole **4a** was found to be an intermediate leading to novel 2,3-fused quinoxalines. This paper describes the ring transformation of the 3-quinoxalinyl-1,5-benzodiazepine **2** into the benzimidazolylmethylenequinoxaline **4a** and the conversions of **4a** into the novel 2,3-condensed quinoxalines having benzimidazole moiety.

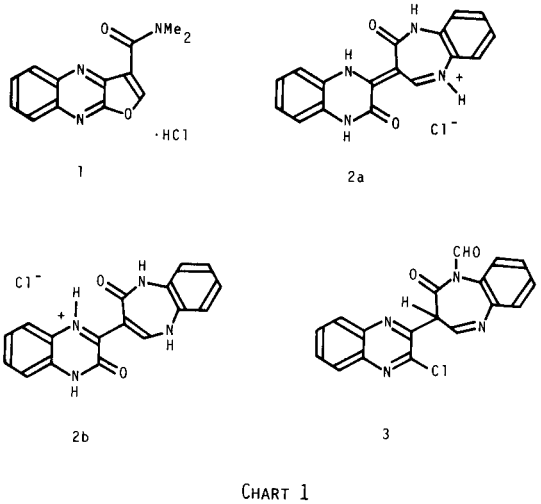
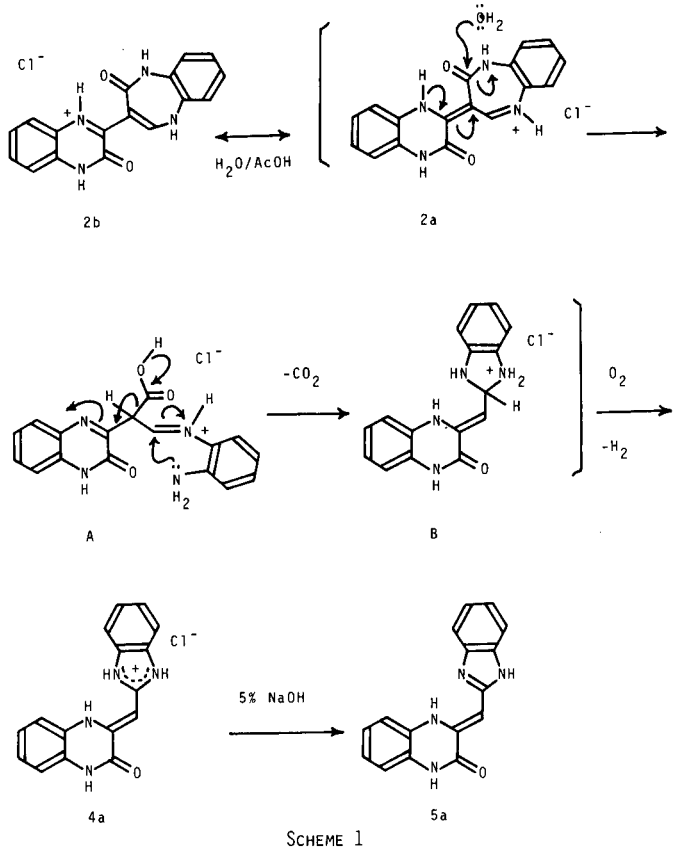
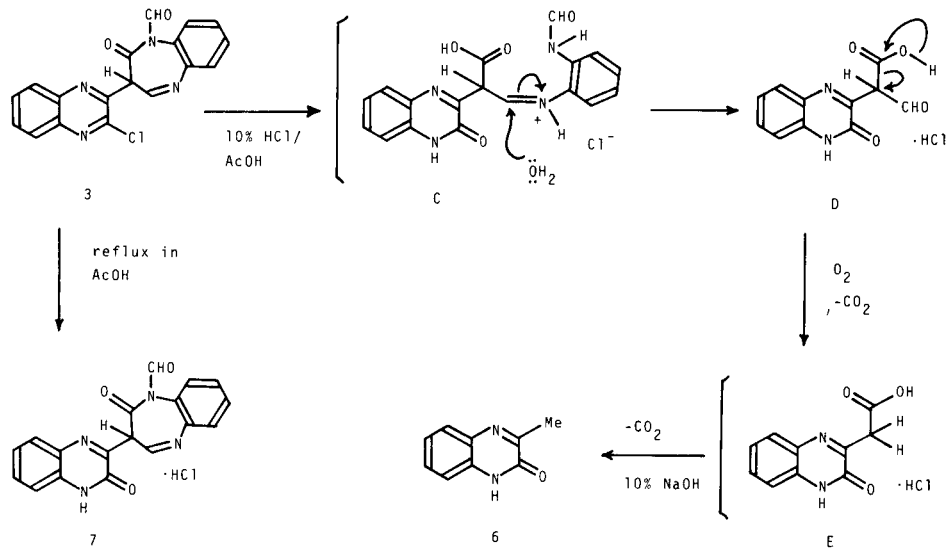


CHART 1



SCHEME 1

Refluxing of **2** in aqueous acetic acid solution effected ring transformation to give **4a** presumably *via* intermediates A and B (Scheme 1), and treatment of **4a** with 5% sodium hydroxide furnished the free base (**5a**). On the other hand, refluxing of **3** in 10% hydrochloric acid/acetic acid resulted in dechlorination and decomposition of the diaz-



SCHEME 2

epine ring to afford **6** [9] presumably *via* intermediates C, D and E (Scheme 2). Since refluxing of **3** in acetic acid effected dechlorination to provide 3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-1-formyl-2-oxo-3*H*--1,5-benzodiazepine hydrochloride (**7**), it was reasonable to speculate the intermediate C. In the intermediate C, there was no cyclization into the benzimidazole ring such as an intermediate F, presumably due to a weak nucleophilic attack of the formyl group-bound nitrogen atom to the imino carbon. Instead of this nitrogen to carbon attack, hydrolysis of the imino bond would take place to pass into the intermediate D.

The structural assignments of **4a** and **5a** were based on the analytical and spectral data. The ^{1}H-nmr spectra of **4a** and **5a** in DMSO-d_6 exhibited the vinyl [δ 6.41 (**4a**) and 6.24 (**5a**) ppm] and methylene [δ 4.78 (**4a**) and 4.55 (**5a**) ppm] proton signals (Table I), whose values were similar to those of the other 3-heteroarylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines [vinyl (δ 6.42-5.87 ppm) and methylene (δ 4.56-4.18 ppm)] previously synthesized by us [4-8]. These data indicated the coexistence of two tautomers **a** and **b** in DMSO-d_6 (Scheme 3) [4-8]. The integral ratios of the vinyl *versus* methylene proton signals are 1:1 in **4a** and 9:1 in **5a** at 30°. In the ^{1}H-nmr spectra of **4a** and **5a** in trifluoroacetic acid (TFA), the methylene proton signals were observed at δ 5.21 and 5.12 ppm, respectively, with disappearance of the vinyl proton signals, indicating the changes of **4a** and **5a** into the species **4c** and **5c**, respectively [4-8]. In addition, the ^{1}H-nmr spectra of **4a** and **5a** in TFA-d_1 exhibited no vinyl, methylene, and NH proton signals, suggesting the formations of the species **4e** and **5e**, respectively [8]. Thus, increase in acidity of the media was shown to promote the equilibria of the vinyl form **a** into the methylene form **b** in the compounds **4a** and **5a**. These results coincide with those reported previously [4-8]. Furthermore, the interesting data were obtained when the ^{1}H-nmr spectra of **4a** and **5a** were measured in DMSO-d_6/deuterium oxide. The ^{1}H-nmr spectrum of **4a** in DMSO-d_6/deuterium oxide exhibited no vinyl and methylene as well as NH proton signals, suggesting the formations of the species **4d** and/or **4e**, while the ^{1}H-nmr spectrum of **5a** in DMSO-d_6/deuterium oxide represented the vinyl (δ 6.24 ppm) and methylene (δ 4.55 ppm) proton signals with disappearance of the NH proton signals, suggesting the productions of the species **5f** and **5g**. The D-H exchanges on

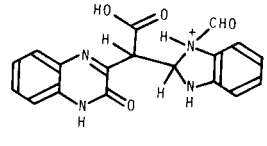


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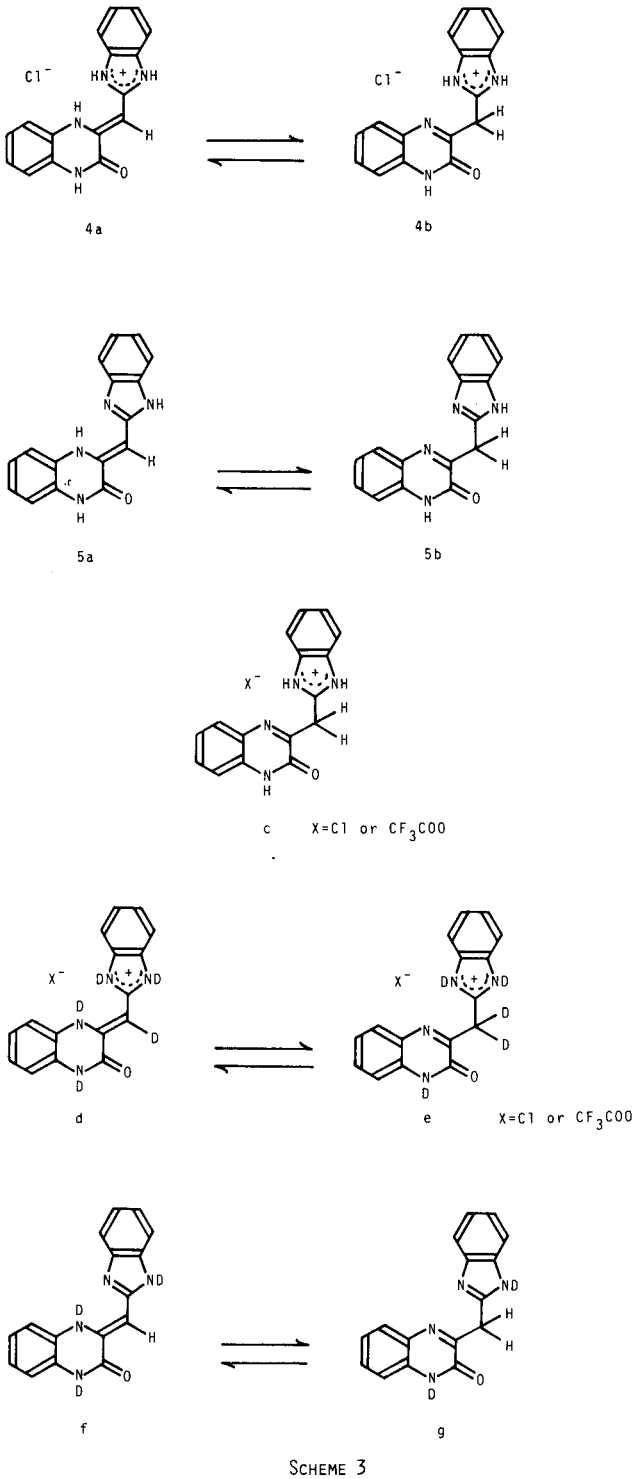
Table 1

Tautomers of **4** and **5** Assigned on the Basis of ^{1}H-NMR Spectral Data

Compound	Solvent	Chemical Shift (δ) Vinyl	Methylene	Tautomer	
4	DMSO-d_6	6.41	4.78	4a	4b [a]
	DMSO-d_6/D_2O	—	—	4d	4e
	TFA	—	5.21	—	4c
	TFA-d_1	—	—	—	4e
5	DMSO-d_6	6.24	4.55	5a	5b [a]
	DMSO-d_6/D_2O	6.24	4.55	5f	5g
	TFA	—	5.12	—	5c
	TFA-d_1	—	—	—	5e

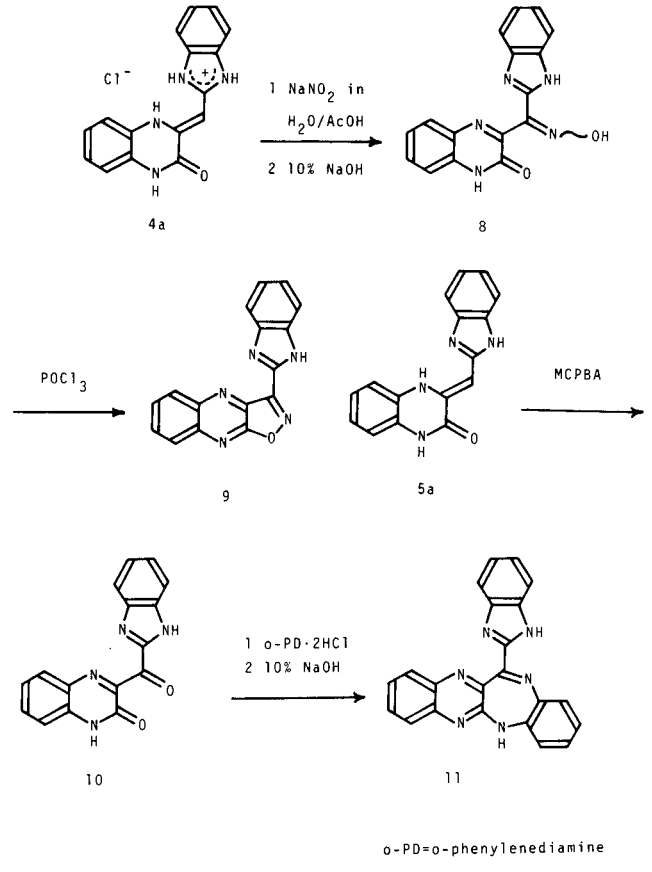
[a] Integral ratios of the vinyl-methylene proton signals are 1:1 (**4**) and 9:1 (**5**) at 30°.



Scheme 3

the methylenic carbon of the hydrochloride **4a** would be mediated with deuterium chloride in the medium, giving the species **4d** and/or **4e**, since such a data was not obtained in the free base **5a**.

Compounds **4a** and **5a** were further converted into the 2,3-fused quinoxalines as follows. The reaction of **4a** with



Scheme 4

nitrous acid resulted in hydroxyimination [5,6] to afford 3-(α-hydroxyiminobenzimidazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxaline (**8**) [9], whose refluxing in phosphoryl chloride effected dehydrative cyclization to provide 3-benzimidazol-2-yl)isoxazolo[4,5-*b*]quinoxaline (**9**). On the other hand, oxidation of **5a** with *m*-chloroperbenzoic acid (MCPBA) [4a,5,6] produced 3-(benzimidazol-2-ylcarbonyl)-2-oxo-1,2-dihydroquinoxaline (**10**). The reaction of **10** with *o*-phenylenediamine dihydrochloride gave 12-(benzimidazol-2-yl)-6*H*-quinoxalino[2,3-*b*][1,5]benzodiazepine (**11**) [9] (Scheme 4).

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded from potassium bromide discs on a JASCO IRA-1 spectrophotometer. The ^{1}H nmr spectra were measured with an EM-390 spectrometer at 90 MHz using tetramethylsilane as an internal reference. Chemical shifts are given in the δ scale, relative to the internal reference. Mass spectra (ms) were determined with a JMS-01S spectrometer (JEOL).

3-(Benzimidazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline Hydrochloride (**4a**).

A solution of **2** (8 g) in water (80 ml)/acetic acid (300 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* left an oily re-

sidue, which was triturated with water gave yellow crystals **4a** (6.88 g, 94%). Recrystallization from ethanol/water afforded yellow needles **4a** as monohydrate, mp 210-212°; ir: ν cm^{-1} 1680, 1638, 1610, 1565, 1555; ms: m/z 276 (M$^+$); ^{1}H-nmr (DMSO-d$_6$): 12.73 (brs, NH) [10], 12.53-12.00 (br, NH, =$^+$NH-) [10], 11.80 (s, NH) [10], 8.10-6.90 (m, 8H, aromatic), 6.41 (s, vinyl) [10], 4.78 (s, methylene) [10], 4.00 (br, water).

Anal. Calcd. for $C_{16}H_{15}ClN_4O_2$: C, 58.09; H, 4.57; N, 16.94. Found: C, 58.29; H, 4.54; N, 16.94.

Free Base **5a**.

Five percent sodium hydroxide was added dropwise to a suspension of **4a** (5 g) in ethanol with heating on a boiling water bath to provide a clear solution, which was filtered. The filtrate was allowed to stand at room temperature, and then yellow needles **5a** precipitated (4.58 g, 93%), mp above 330°; ir: ν cm^{-1} 1670, 1625, 1605, 1595, 1580, 1520; ms: m/z 276 (M$^+$); ^{1}H-nmr (DMSO-d$_6$): 12.30 (s, 2H, NH), 11.33 (s, 1H, NH), 7.90 (m, 2H, aromatic), 7.33-6.77 (m, 6H, aromatic), 6.24 (s, 1H, vinyl), 4.55 (s, methylene) [10], 3.33 (br, water).

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.31; H, 4.38; N, 20.27.

3-Methyl-2-oxo-1,2-dihydroquinoxaline (**6**).

A solution of **3** (2 g) in 10% hydrochloric acid (20 ml)/acetic acid (80 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* gave crystals as hydrochloride, which was treated with hot 10% sodium hydroxide/ethanol to provide a clear solution. Evaporation of the solvent *in vacuo* afforded yellow crystals as free base, and the product **6** was taken up in hot ethanol and filtered. Cooling of the filtrate at room temperature precipitated yellow needles **6** (290 mg, 32%); ir spectrum and melting point of this sample coincided with those of an authentic sample [11].

3-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-1-formyl-2-oxo-3*H*-1,5-benzodiazepine Hydrochloride (**7**).

A suspension of **3** (5 g) in acetic acid (300 ml) was refluxed in an oil bath for 2 hours to precipitate orange needles **7**, which were collected by suction filtration. Trituration with hot ethanol gave an analytically pure sample **7** (3.92 g, 75%), mp 273-274°; ir: ν cm^{-1} 1765, 1720, 1690, 1625; ms: m/z 332 (M$^+$); ^{1}H-nmr (DMSO-d$_6$): 13.40 (brs, 1H, NH), 11.08 (s, 1H, CHO), 9.70-9.00 (m, 1H, aromatic), 8.90 (brs, 1H, =$^+$NH-), 8.72 (d, J = 14.7 Hz, 1H, C$_4$-H) [12], 8.20-6.67 (m, 7H, aromatic), 7.54 (d, J = 14.7 Hz, 1H, C$_3$-H) [12].

Anal. Calcd. for $C_{18}H_{13}ClN_4O_3$: C, 58.63; H, 3.55; N, 15.19. Found: C, 58.34; H, 3.62; N, 14.98.

3-(α-Hydroxyiminobenzimidazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxaline (**8**).

A solution of sodium nitrite (1.33 g, 19.2 mmoles) in water (30 ml) was added dropwise to a suspension of **4a** (4 g, 12.8 mmoles) in acetic acid (120 ml)/water (10 ml) with stirring in an ice-water bath. The mixture was heated on a boiling water bath for 1 hour to give a clear solution. Evaporation of the solvent *in vacuo* left an oily residue, which was dissolved in ethanol/water (1:10 v/v). Ten percent sodium hydroxide was added to the solution to adjust *p*H near 7.0. Removal of the solvent by evaporation *in vacuo* afforded yellow crystals **8**, which were collected by suction filtration (3.78 g, 91%). Recrystallization from ethanol/water provided a yellow powder as monohydrate, mp 240° dec; ir: ν cm^{-1} 1650, 1605, 1540, 1480, 1420; ms: m/z 305 (M$^+$); ^{1}H-nmr (DMSO-d$_6$): 12.87 (s, 1H, NH), 12.23 (brs, 1H, NH), 12.87-12.23 (br, 1H, OH), 8.00-6.90 (m, 8H, aromatic), 3.33 (br, water).

Anal. Calcd. for $C_{16}H_{13}N_5O_3$: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.70; H, 3.97; N, 21.62.

3-(Benzimidazol-2-yl)isoxazolo[4,5-*b*]quinoxaline (**9**).

A solution of **8** (1 g) in phosphorus oxychloride (10 ml)/dioxane (10 ml) was refluxed in an oil bath for 1 hour. The solution was cooled to room temperature and then poured onto crushed ice to precipitate yellow crystals **9**, which were collected by suction filtration (0.90 g, 96%). Recrystallization from ethanol/water provided yellow needles as halfhydrate, mp 248-250°; ir: ν cm^{-1} 3270, 1615, 1585, 1555, 1495, 1475, 1425; ms: m/z 287 (M$^+$); ^{1}H-nmr (DMSO-d$_6$): 12.38 (br, 1H, NH), 8.67-7.23 (m, 8H, aromatic) 3.30 (br, water).

Anal. Calcd. for $C_{16}H_9N_5O\cdot\frac{1}{2}H_2O$: C, 64.85; H, 3.40; N, 23.64. Found: C, 65.14; H, 3.11; N, 23.92.

3-(Benzimidazol-2-ylcarbonyl)-2-oxo-1,2-dihydroquinoxaline (**10**).

A solution of **5a** (5 g, 18.1 mmoles) and MCPBA (2.5 equivalents) in ethanol (300 ml) was refluxed on a boiling water bath for 2 hours. Evaporation of the solvent *in vacuo* afforded crystals, which were dissolved in a small amount of chloroform and filtered. Cooling of the filtrate at room temperature precipitated yellow crystals **10** (2.71 g, 49%). Recrystallization from chloroform provided yellow needles as monohydrate, mp 175-177°; ir: ν cm^{-1} 3040, 2960, 2870, 1660, 1605; ms: m/z 290 (M$^+$); ^{1}H-nmr (DMSO-d$_6$): 12.90 (brs, 1H, NH), 11.87 (s, 1H, NH), 8.00-6.90 (m, 8H, aromatic), 3.37 (br, water).

Anal. Calcd. for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.18. Found: C, 62.22; H, 3.82; N, 17.96.

12-(Benzimidazol-2-yl)-6*H*-quinoxalino[2,3-*b*][1,5]benzodiazepine (**11**).

A solution of **10** (700 mg, 2.27 mmoles) and *o*-phenylenediamine dihydrochloride (960 mg, 3.41 mmoles) in acetic acid (50 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* left an oily residue, which was dissolved in hot ethanol. Ten percent sodium hydroxide was added to the solution to adjust *p*H near 7.0, and yellow crystals precipitated were collected by suction filtration. Recrystallization from ethanol afforded yellow needles as ethanol-complex (250 mg, 27%), mp 327-328°; ir: ν cm^{-1} 3040, 2950, 2870, 1610, 1575, 1510, 1470, 1450, 1410; ms: m/z 316 (M$^+$); ^{1}H-nmr (DMSO-d$_6$): 12.55 (s, 2H, NH), 8.40-7.00 (m, 12H, aromatic), 4.27 (brs, 1H, OH of ethanol), 3.43 (q, J = 7 Hz, 2H, CH$_2$ of ethanol), 1.04 (t, J = 7 Hz, 3H, Me of ethanol).

Anal. Calcd. for $C_{24}H_{20}N_6O$: C, 70.57; H, 4.94; N, 20.58. Found: C, 70.32; H, 4.82; N, 20.49.

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[8] Y. Kurasawa, Y. Okamoto and A. Takada, *Chem. Pharm. Bull.*, **33**, 1249 (1985).

[9] Compounds **6**, **8** and **11** were obtained after treatment with base (*cf.* Experimental).

[10] Because of the tautomerism, the integral curves of NH, vinyl and methylene proton signals were unsatisfactorily observed.

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[12] These signals were checked by a decoupling procedure.