RING TRANSFORMATION OF A 3-QUINOXALINYL-1,5-BENZODIAZEPINE INTO NOVEL 3-(BENZIMIDAZOL-2-YLMETHYLENE)-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINE. CONVENIENT SYNTHESIS OF NOVEL 2,3-FUSED QUINOXALINES

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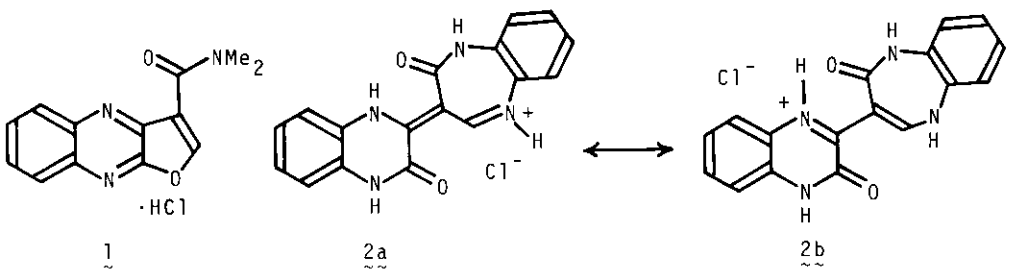
Abstract —— Ring transformation of the 3-quinoxalinyl-1,5-benzodiazepine hydrochloride (2) gave novel 3-(benzimidazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline hydrochloride (3a), whose treatment with 5% NaOH afforded the free base (4a). Compounds 3a and 4a were converted into the 2,3-fused quinoxalines (6 and 8) via the oxime (5) and ketone (7), respectively.

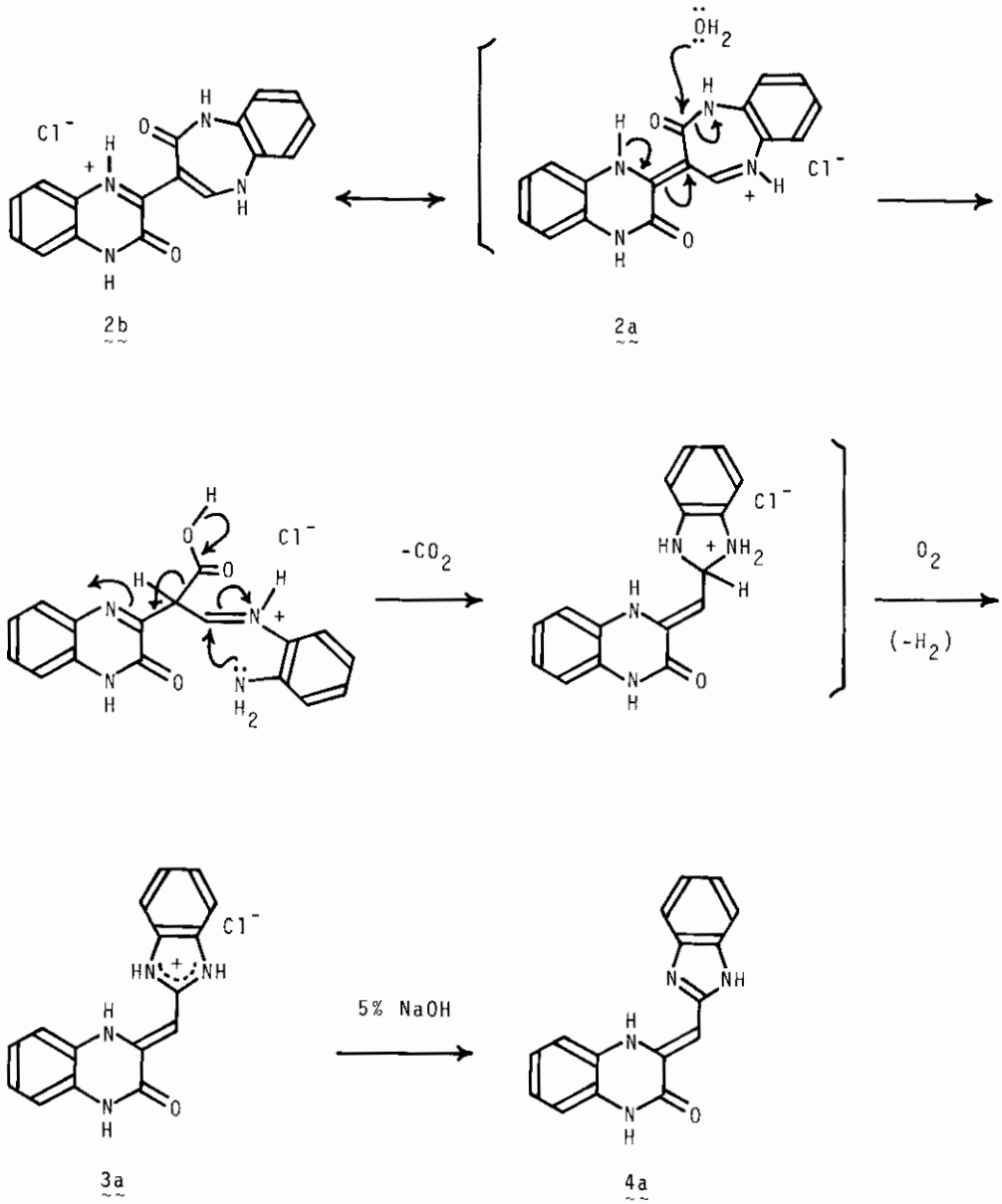
In a previous paper,[1] we reported a ring transformation of 3-(N,N-dimethylcarbamoyl)-furo[2,3-b]quinoxaline hydrochloride (1) into the 3-quinoxalinyl-1,5-benzodiazepine hydrochloride (2) (Scheme 1). Some 1,5-benzodiazepines have been transformed into



1 2a 2b

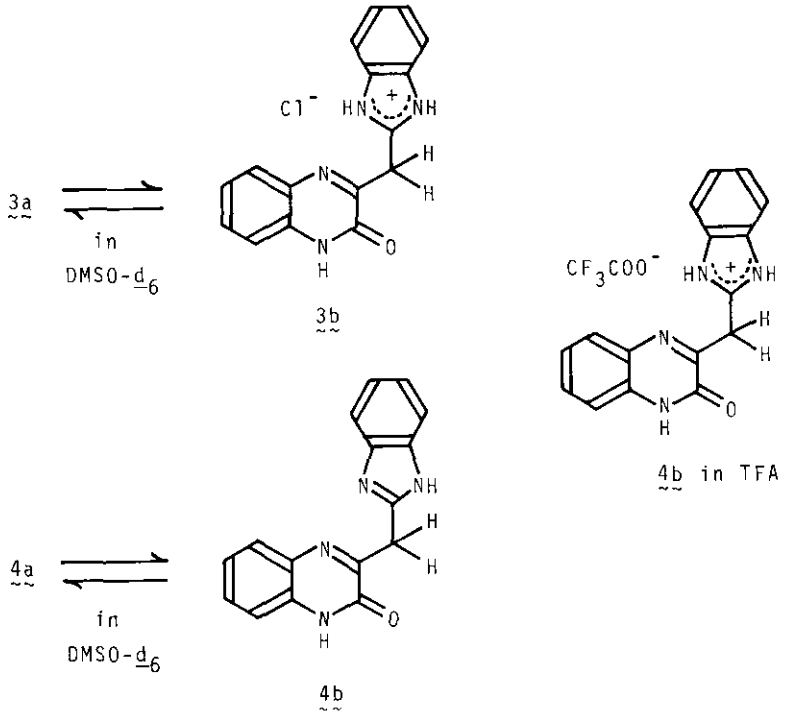
SCHEME 1

benzimidazoles under acidic conditions,[2] and hence the 1,5-benzodiazepine ring of 2 is expected to be converted into the benzimidazole ring. This successful ring



SCHEME 2

transformation would enable us to produce a new heterocyclic ring system. Thus, the ring transformation of 2 provided novel 3-(benzimidazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline. In addition, this compound was found to be a key intermediate leading to novel 2,3-fused quinoxalines. This paper describes the conversion of the 3-quinoxalinyl-1,5-benzodiazepine into the 2,3-condensed quino-

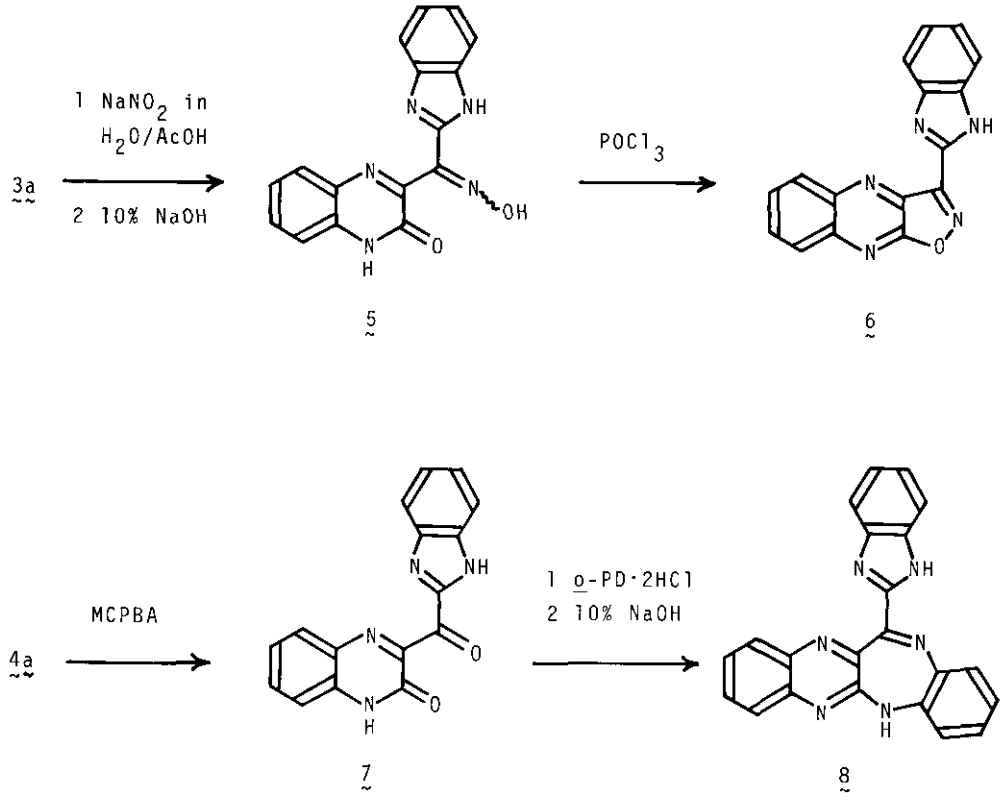


SCHEME 3

Table I. Tautomers of 3 and 4 assigned by ^{1}H-NMR Spectral Data

Compound	Solvent	Tautomer	
3	DMSO-d_6	3a	3b*
	TFA	—	3b
4	DMSO-d_6	4a	4b*
	TFA	—	4b

* Integral ratios of the vinyl-methylene proton signals are 1:1 (3) and 9:1 (4) at 30 °C.



SCHEME 4

xalines (6,8).

Refluxing of 2 (8 g) in H_2O (80 ml)/AcOH (300 ml) for 2 h gave 3-(benzimidazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline hydrochloride (3a) (6.88 g, 94 %).[3] Treatment of 3a (5 g) with 5% NaOH afforded the free base (4a) (4.58 g, 93 %).[4] These results are shown in Scheme 2, including a postulated reaction mechanism. Structural assignments of 3a and 4a were based on the analytical and spectral data. The NMR spectra of 3a and 4a in DMSO-d_6 exhibited the vinyl [δ 6.41 (3a) and 6.24 (4a) ppm] and methylene [δ 4.78 (3a) and 4.55 (4a) ppm] proton signals, whose values were similar to those of the other 3-heteroarylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines previously synthesized by us [vinyl (δ 6.42-5.87 ppm), methylene (δ 4.56-4.18 ppm)].[5-8] These data indicate the coexistence of two tautomers a and b in DMSO-d_6 (Scheme 3, Table I).[5-8] Moreover, the spectra of 3a

and 4a in trifluoroacetic acid (TFA) represented the methylene proton signals at δ 5.21 and 5.12 ppm due to the tautomers 3b and 4b, respectively, without the vinyl proton signals.[5-8]

The reaction of 3a (4 g, 12.8 mmol) with $NaNO_2$ (1.33 g, 19.2 mmol) in H_2O (40 ml)/AcOH (120 ml) resulted in hydroxyimination[6,7] to provide 3-(α-hydroxyimino-benzimidazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxaline (5) (3.78 g, 91%).[9] Refluxing of 5 (1 g) in $POCl_3$ (10 ml)/dioxane (10 ml) effected dehydrative cyclization to furnish 3-(benzimidazol-2-yl)isoxazolo[4,5-b]quinoxaline (6) (0.90 g, 96%).[10] On the other hand, oxidation of 4a (5 g) with m-chloroperbenzoic acid (MCPBA) (2 eq.) in EtOH (300 ml)[5a,6,7] produced 3-(benzimidazol-2-ylcarbonyl)-2-oxo-1,2-dihydroquinoxaline (7) (2.71 g, 49%).[11] Refluxing of 7 (700 mg, 2.27 mmol) and o-phenylenediamine (o-PD) dihydrochloride (960 mg, 3.41 mmol) in AcOH (50 ml) followed by treatment with 10% NaOH afforded 12-(benzimidazol-2-yl)-6H-quinoxalino[2,3-b][1,5]benzodiazepine (8) (250 mg, 27%).[12]

REFERENCES AND FOOTNOTES

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3. 3a: Recrystallization from EtOH/H_2O gave yellow needles as monohydrate, mp 210-212 °C. IR ν(KBr): 1680, 1630, 1610, 1565, 1555 cm^{-1}. MS m/z: 276 (M^+). NMR (DMSO-d_6) δ: 12.73 (br s, NH),[13] 12.53-12.00 (br, NH, =$\overset{+}{N}$H-),[13] 11.80 (s, NH),[13] 8.10-6.90 (m, 8H, aromatic), 6.41 (s, vinyl),[13] 4.78 (s, methylene),[13] 4.00 (br, H_2O). 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.

4. 4a: Recrystallization from EtOH afforded yellow needles, mp above 330 °C. IR ν(KBr): 3280, 3000, 2960, 2880, 2840, 1670, 1625, 1605, 1595, 1580, 1520 cm^{-1}. MS m/z: 276 (M^+). NMR (DMSO-d_6) δ: 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),[13] 3.33 (br, H_2O). 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.

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9. 5: Recrystallization from EtOH/H_2O provided a yellow powder as monohydrate, mp 240 °C (dec.). IR ν(KBr): 1650, 1605, 1540, 1480, 1420 cm^{-1}. MS m/z: 305 (M^+). NMR (DMSO-d_6) δ: 12.87 (s, 1H, NH), 12.23 (br s, 1H, NH), 12.87-12.23 (br, 1H, OH), 8.00-6.90 (m, 8H, aromatic), 3.33 (br, H_2O). 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.

10. 6: Recrystallization from EtOH/H_2O furnished yellow needles as halfhydrate, mp 248-250 °C. IR ν(KBr): 3270, 1615, 1585, 1555, 1495, 1475, 1425 cm^{-1}. MS m/z: 287 (M^+). NMR (DMSO-d_6) δ: 12.38 (br, 1H, NH), 8.67-7.23 (m, 8H, aromatic), 3.36 (br, H_2O). Anal. Calcd for $C_{16}H_9N_5O \cdot 1/2\ H_2O$: C, 64.85; H, 3.40; N, 23.64. Found: C, 65.14; H, 3.11; N, 23.92.

11. 7: Recrystallization from $CHCl_3$ gave yellow needles as monohydrate, mp 175-177 °C. IR ν(KBr): 3040, 2960, 2870, 1660, 1605 cm^{-1}. MS m/z: 290 (M^+). NMR (DMSO-d_6) δ: 12.90 (br s, 1H, NH), 11.87 (s, 1H, NH), 8.00-6.90 (m, 8H, aromatic), 3.37 (br, H_2O). 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, 17.95.

12. 8: Recrystallization from EtOH provided yellow needles as EtOH-complex, mp 327-328 °C. IR ν(KBr): 3040, 2950, 2870, 1610, 1575, 1510, 1470, 1450, 1410 cm^{-1}. MS m/z: 316 (M^+). NMR (DMSO-d_6) δ: 12.55 (s, 2H, NH), 8.40-7.00 (m, 12H, aromatic), 4.27 (br s, 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.

13. Because of the tautomerism, the integral curves of the NH, vinyl, and methylene proton signals are unsatisfactorily observed.

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