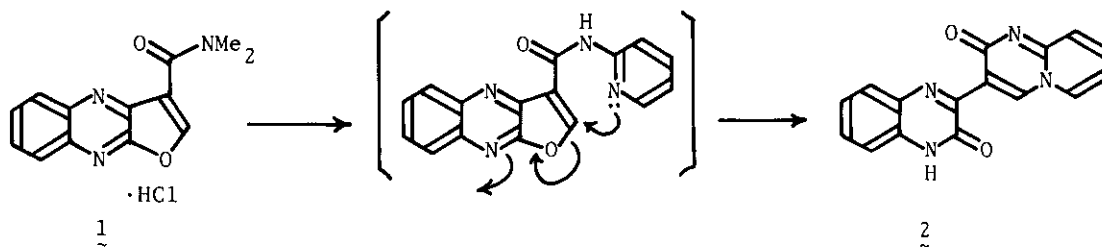


A CONVENIENT SYNTHESIS OF NOVEL 3-QUINOXALINYL-1,5-BENZODIAZEPINES.
STABLE TAUTOMERS IN 1,5-BENZODIAZEPIN-2-ONE RING SYSTEM

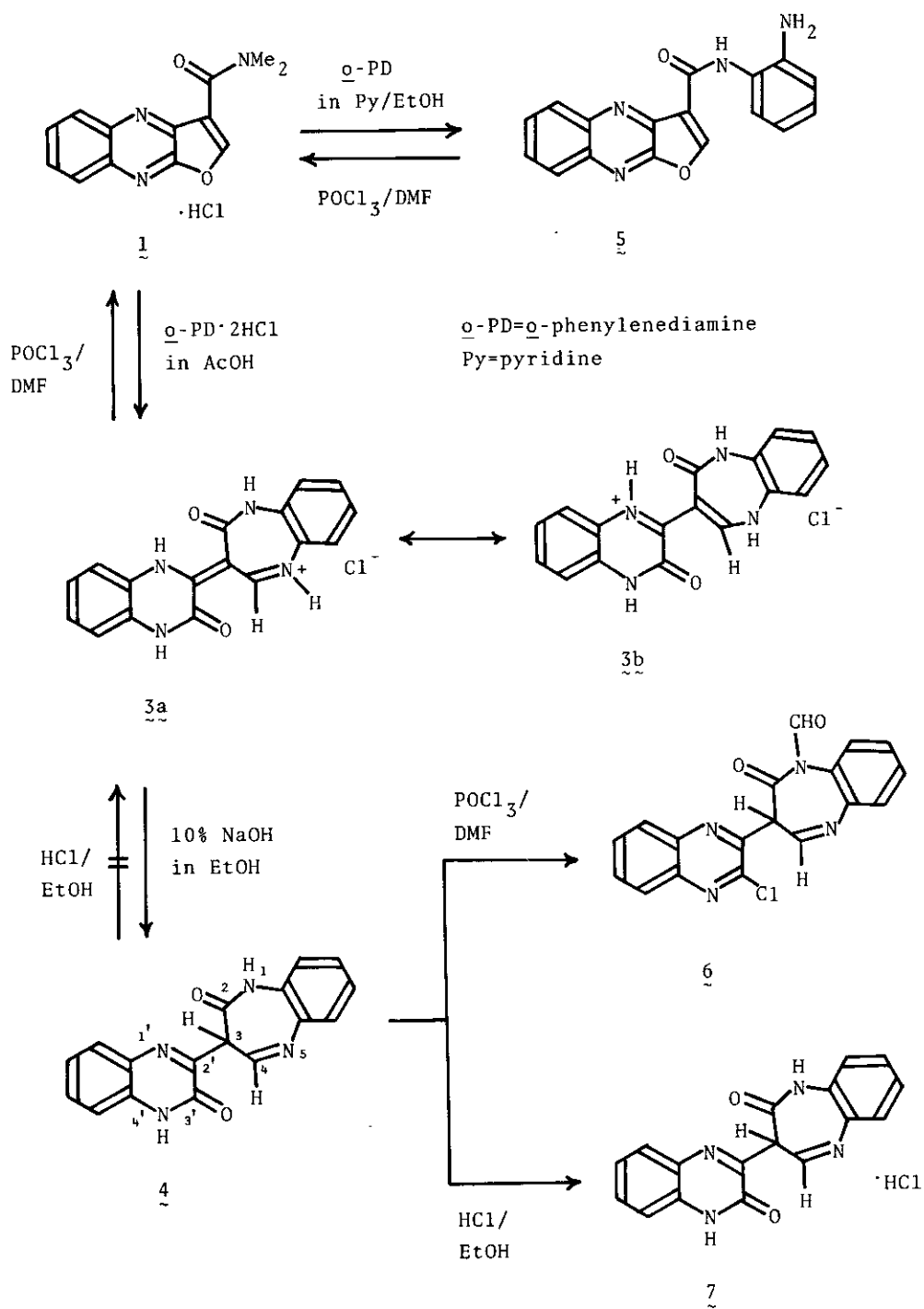
Yoshihisa Kurasawa,* Jun Satoh, Mie Ogura,
Yoshihisa Okamoto, and Atsushi Takada
School of Pharmaceutical Sciences, Kitasato University
Shirokane, Minato-ku, Tokyo 108, Japan

Abstract ----- Various 3-quinoxaliny1-1,5-benzodiazepines (3,4,6,7) were prepared via the ring transformation of 3-(N,N-dimethylcarbamoyl)furo[2,3-b]quinoxaline hydrochloride (1). The hydrochlorides 3 and 7 are the tautomers of the N₁- or N₅-H form and C₃-H form, respectively, which are stable in solid and solution.

In a previous paper,¹ we reported that the reaction of 3-(N,N-dimethylcarbamoyl)-furo[2,3-b]quinoxaline hydrochloride (1) with 2-aminopyridine effected a ring transformation to give the quinoxaliny1pyridopyrimidine (2) (Scheme 1). In this case, a use of *o*-phenylenediamine in place of 2-aminopyridine was expected to induce the ring transformation into a quinoxaliny1-1,5-benzodiazepine, which would become an intermediate to analogues of pharmacologically active heteroepines.² Thus, this paper describes the synthesis of novel quinoxaliny1-1,5-benzodiazepines.



Scheme 1

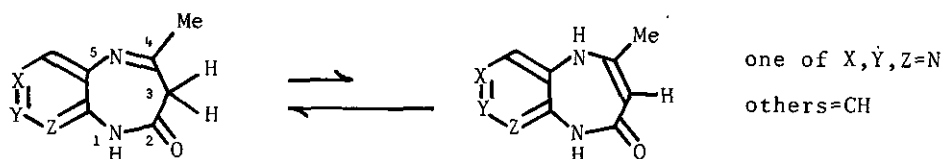


Scheme 2

The reaction of 1 (10 g, 36.0 mmol) with *o*-phenylenediamine dihydrochloride (9.77 g, 54.0 mmol) in AcOH (300 ml) under reflux for 1 h resulted in the formation of 3-(3-oxo-1,2,3,4-tetrahydroquinoxalin-2-ylidene)-1,2-dihydro-2-oxo-3H-1,5-benzodiazepine hydrochloride (3a) or 3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-5H-1,5-benzodiazepine hydrochloride (3b) (7.65 g, 71.7%) as a red powder.³ Treatment of 3 (5 g) with 10% NaOH in EtOH (500 ml) gave the free base 3-(3-oxo-3,4-dihydroquinoxalin-2-yl)-1,2-dihydro-2-oxo-3H-1,5-benzodiazepine (4) (4 g, 90.9%) as yellow needles.⁴ On the other hand, the reaction of 1 (5 g, 18.0 mmol) with *o*-phenylenediamine (2.92 g, 27.0 mmol) in pyridine (20 ml)/EtOH (400 ml) under reflux for 1 h did not afford 4, but provided 3-(N-2-aminophenylcarbonyl)furo[2,3-*b*]quinoxaline (5) (4.44 g, 81%) as orange needles.⁵ Refluxing of 5 in pyridine/butanol, trifluoroacetic acid (TFA)/acetic acid, or TFA/butanol seldom gave 4. Interestingly, moreover, the reaction of 3 (1 g) and 5 (1 g) with POCl₃ (10 ml)/DMF (10 ml) under heating on a boiling water bath for 2 h produced 1 (450 mg, 55% from 3; 200 mg, 22% from 5), while a similar reaction of 4 (1 g) with POCl₃ (50 ml)/DMF (50 ml) for 5 h effected chlorination and formylation to afford 3-(3-chloroquinoxalin-2-yl)-1,2-dihydro-1-formyl-2-oxo-3H-1,5-benzodiazepine (6) (300 mg, 26%) as yellow needles.⁶ The difference in the reactivity between 3 and 4 is rationalized by the following hydrochloride formation. Treatment of 4 (440 mg) with ethanolic HCl (200 ml) under ice-cooling did not provide the hydrochloride 3, but resulted in the formation of the different hydrochloride 7 (480 mg, 97.6%) as a red powder.⁷

There have been reported many examples on the tautomerism of the 1,5-aryldiazepin-2-one ring system, wherein the most of compounds predominantly exist as the C₃-H form (A) rather than the N₅-H form (B), as shown in Scheme 3.⁸ Among our compounds, 4, 6, and 7 were found to predominate in the C₃-H form, which was confirmed by the presence of the coupling between the C₃-H and C₄-H protons. The ¹³C-NMR spectral data of 4 also assured the presence of the tertiary C₃-carbon, which was observed as the doublet signal at δ 108.92 ppm. Interestingly, furthermore, 3 was found to exist stably in solid and solution, and it did not isomerize into 7. The C₄-H proton of 3 was observed as the singlet signal, elucidating the presence of the quaternary C₃-carbon. In the IR spectra, the ν_{C=O} of 3 and 7 appeared at a different wavenumber area.

The structural elucidation of 5 was based on the ¹H-NMR and IR spectral data. Espe-



Scheme 3

cially, its IR spectrum exhibited the 3-carbamoyl absorption band at a high wave-number area [1840, 1800 cm^{-1} (branched)], which was characteristic in the furo-[2,3-*b*]quinoxaline 3-carbamoyl derivatives.⁹ On the other hand, the structural assignment of **6** was mainly based on the ^1H -NMR spectral data. Namely, one of the eight aromatic protons in **3**, **4**, and **7** were observed at a lower magnetic field than the seven other aromatic protons, while the eight aromatic protons of **5** and **6** were observed separately as two groups of five and three protons. This difference would be due to whether the quinoxaline ring was aromatized or not.

REFERENCES AND FOOTNOTES

1. Y. Kurasawa and A. Takada, *Heterocycles*, 1980, **14**, 611; Idem, *Chem. Pharm. Bull.*, 1980, **28**, 3537.
2. R. I. Fryer, W. Leimgruber, and E. J. Trybulski, *J. Med. Chem.*, 1982, **25**, 1050; Y. Nagai, A. Irie, H. Nakamura, K. Hino, H. Uno, and H. Nishimura, *ibid.*, 1982, **25**, 1065; S. Kaspararek, *Ad. Heterocyclic Chem.*, 1974, **17**, 45; A. C. Playle, *Drugs of the Future*, 1976, **1**, 511; L. H. Sternbach, *Angew. Chem. Int. Ed.*, 1971, **10**, 34.
3. **3**: Washing with hot EtOH/H₂O gave an analytically pure red powder, mp 266-267 °C. IR $\nu(\text{KBr})$ 1680, 1635 cm^{-1} . MS m/z : 304 (M^+). ^1H -NMR $\delta(\text{DMSO}-d_6)$ 12.67 (s, 1H, NH), 11.50 (br, 1H, NH), 9.67 (s, 1H, NH), 8.42 (s, 1H, C₄-H), 7.69 (d, dd, $J_{\text{ortho}}=9$ Hz, $J_{\text{meta}}=J_{\text{para}}=1$ Hz, 1H, aromatic), 7.57-6.83 (m, 7H, aromatic), 6.50 (br, 1H, =NH-). Anal. Calcd for C₁₇H₁₃ClN₄O₂: C, 59.92; H, 3.84; Cl, 10.40; N, 16.44. Found: C, 59.64; H, 3.84; Cl, 10.34; N, 16.14.
4. **4**: Recrystallization from EtOH afforded yellow needles, mp 325-326 °C (dec.).

IR ν (KBr) 1735, 1680, 1650 cm^{-1} . MS m/z : 304 (M^+). $^1\text{H-NMR}$ δ (DMSO- d_6) 12.33 (s, 1H, NH), 11.27 (s, 1H, NH), 8.55 (d, $J=15$ Hz, 1H, $C_4\text{-H}$), ** 7.73 (dd, $J_{\text{ortho}}=9$ Hz, $J_{\text{meta}}=1.8$ Hz, 1H, aromatic), 7.46 (d, $J=15$ Hz, 1H, $C_3\text{-H}$), ** 7.67-7.00 (m, 7H, aromatic). $^{13}\text{C-NMR}$ δ (DMSO- d_6) 155.42 (s, 1C), 154.06 (s, 1C), 153.63 (s, 1C), 133.19 (s, 1C), 132.12 (s, 1C), 129.99 (d, 1C), 129.99 (d, 1C), 129.79 (s, 1C), 128.77 (d, 1C), 128.29 (s, 1C), 124.16 (d, 1C), 124.01 (d, 1C), 122.36 (d, 1C), 116.00 (d, 1C), 110.91 (d, 1C), 110.52 (d, 1C), 108.92 (d, 1C). Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_2$: C, 67.09; H, 3.98; N, 18.41. Found: C, 66.85; H, 3.97; N, 18.19.

5. 5: Washing with hot EtOH provided analytically pure orange needles, mp 205-208 °C. IR ν (KBr) 3420, 3360, 1840, 1800, 1660, 1640 cm^{-1} . MS m/z : 304 (M^+). $^1\text{H-NMR}$ δ (DMSO- d_6) 8.62 (s, 1H, $C_2\text{-H}$), 8.00-7.40 (m, 5H, aromatic), 7.20-6.57 (m, 3H, aromatic), 5.67-3.33 (br, NH, NH_2 , and H_2O). Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_2$: C, 67.09; H, 3.98; N, 18.41. Found: C, 66.93; H, 4.08; N, 18.12.
6. 6: Recrystallization from EtOH/ CHCl_3 gave yellow needles, mp 246-248 °C. IR ν (KBr) 1750, 1725, 1700, 1640, 1610 cm^{-1} . MS m/z : 350 (M^+), 352 (M^++2). $^1\text{H-NMR}$ δ (CF_3COOH) 9.42 (s, 1H, CHO), 8.75 (d, $J=15$ Hz, 1H, $C_4\text{-H}$), ** 8.43-7.97 (m, 5H, aromatic), 8.02 (d, $J=15$ Hz, 1H, $C_3\text{-H}$), ** 7.70-7.23 (m, 3H, aromatic). Anal. Calcd for $\text{C}_{18}\text{H}_{11}\text{ClN}_4\text{O}_2$: C, 61.64; H, 3.16; Cl, 10.11; N, 15.97. Found: C, 61.53; H, 3.15; Cl, 10.23; N, 15.88.
7. 7: Washing with EtOH and hexane afforded an analytically pure red powder, mp 292-293 °C. IR ν (KBr) 1740, 1680, 1620 cm^{-1} . MS m/z : 304 (M^+). $^1\text{H-NMR}$ δ (DMSO- d_6) 12.57 (br, 1H, NH), 11.51 (s, 1H, NH), 8.77 (br, 1H, $=\text{NH-}$), 8.75 (d, $J=15$ Hz, 1H, $C_4\text{-H}$), ** 7.80 (d, $J=7$ Hz, 1H, aromatic), 7.55 (d, $J=15$ Hz, 1H, $C_3\text{-H}$), ** 7.73-7.00 (m, 7H, aromatic). Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{ClN}_4\text{O}_2$: C, 59.92; H, 3.84; Cl, 10.40; N, 16.44. Found: C, 59.81; H, 3.63; Cl, 10.59; N, 16.18.
8. J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, Adv. Heterocyclic Chem., Suppl. 1, "The Tautomerism of Heterocycles," pp 560-564.
9. Y. Kurasawa and A. Takada, Heterocycles, 1980, 14, 281; Idem, Chem. Pharm. Bull., 1981, 29, 2871.

** determined by decoupling

Received, 12th April, 1984