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

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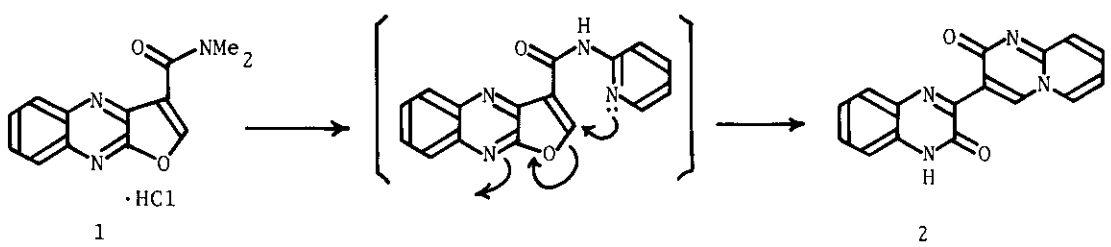
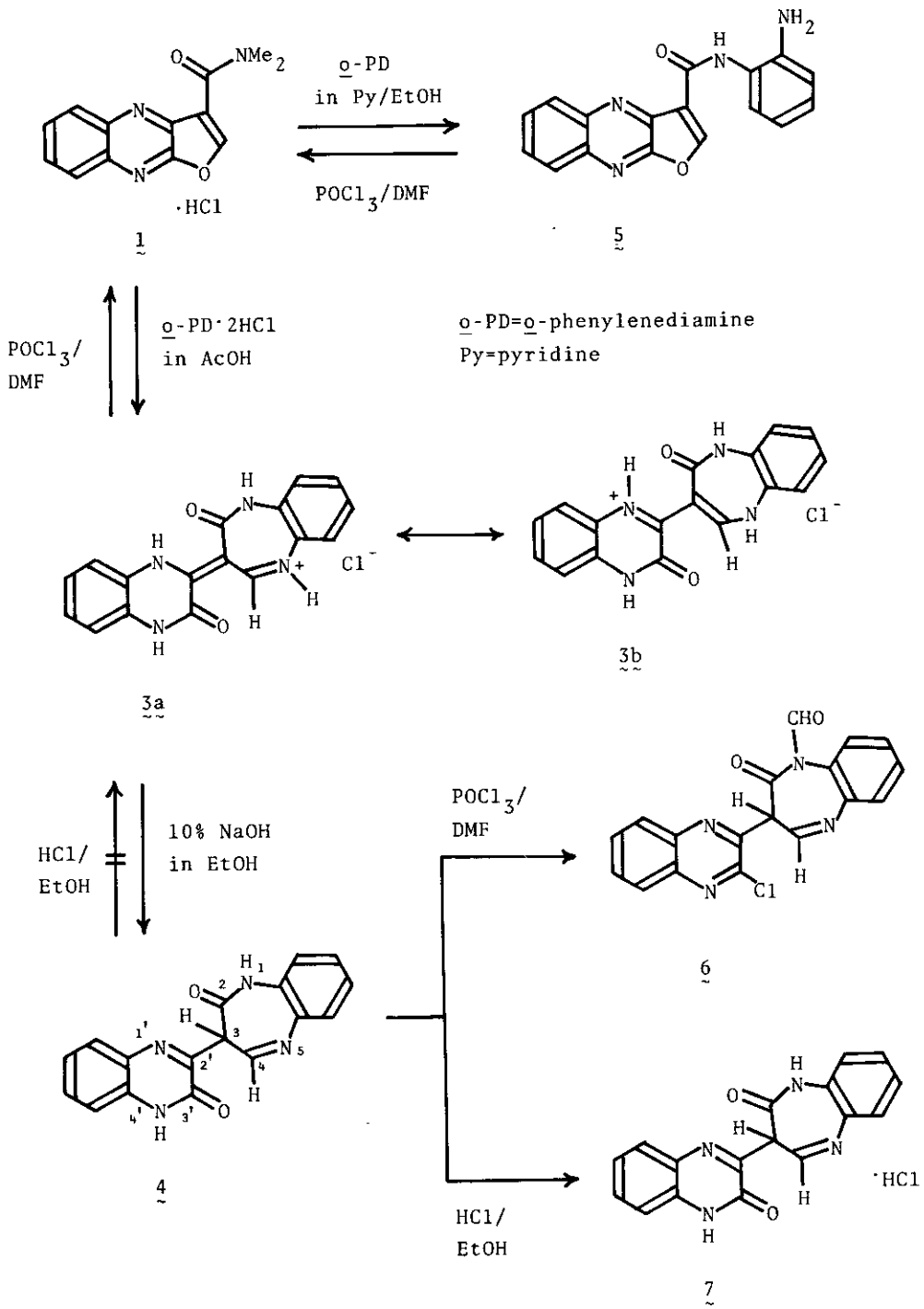
Abstract ——— Various 3-quinoxalinyl-1,5-benzodiazepines (3,4,6, 7) were prepared via the ring transformation of 3-(N,N-dimethylcarbamoyl)furo[2,3-b]quinoxaline hydrochloride (1). The hydrochlorides 3 and 7 are the tautomers of the N_1,- or N_5-H form and C_3-H form, respectively, which are stable in 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 quinoxalinylpyridopyrimidine (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 quinoxalinyl-1,5-benzodiazepine, which would become an intermediate to analogues of pharmacologically active heteroepines.[2] Thus, this paper describes the synthesis of novel quinoxalinyl-1,5-benzodiazepines.



1 2

Scheme 1

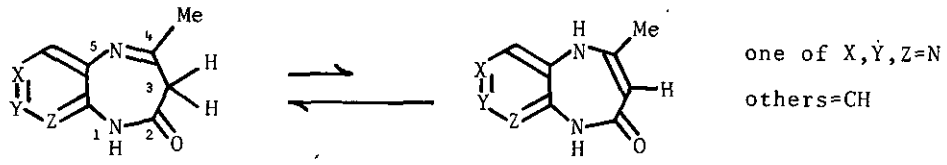

o-PD
in Py/EtOH
POCl3/DMF
·HCl
1
5
o-PD·2HCl
in AcOH
POCl3/
DMF
o-PD=o-phenylenediamine
Py=pyridine
3a
3b
HCl/
EtOH
10% NaOH
in EtOH
4
POCl3/
DMF
HCl/
EtOH
6
7
·HCl

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-aminophenylcarbamoyl)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 $POCl_3$ (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 $POCl_3$ (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 C_3-H form (A) rather than the N_5-H form (B), as shown in Scheme 3.[8] Among our compounds, 4, 6, and 7 were found to predominate in the C_3-H form, which was confirmed by the presence of the coupling between the C_3-H and C_4-H protons. The ^{13}C-NMR spectral data of 4 also assured the presence of the tertiary C_3-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 C_4-H proton of 3 was observed as the singlet signal, elucidating the presence of the quarternary C_3-carbon. In the IR spectra, the $\nu_{C=O}$ of 3 and 7 appeared at a different wavenumber area.

The structural elucidation of 5 was based on the ^{1}H-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 ^{1}H-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

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3. 3: Washing with hot EtOH/H_2O gave an analytically pure red powder, mp 266-267 °C. IR ν(KBr) 1680, 1635 cm^{-1}. MS m/z: 304 (M^+). ^{1}H-NMR δ(DMSO-d_6) 12.67 (s, 1H, NH), 11.50 (br, 1H, NH), 9.67 (s, 1H, NH), 8.42 (s, 1H, C_4-H), 7.69 (d, dd, J_{ortho}=9 Hz, J_{meta}=J_{para}=1 Hz, 1H, aromatic), 7.57-6.83 (m, 7H, aromatic), 6.50 (br, 1H, =NH-). Anal. Calcd for $C_{17}H_{13}ClN_4O_2$: 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}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-H),** 7.73 (dd, J_{ortho}= 9 Hz, J_{meta}=1.8 Hz, 1H, aromatic), 7.46 (d, J=15 Hz, 1H, C_3-H),** 7.67-7.00 (m, 7H, aromatic). ^{13}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 $C_{17}H_{12}N_4O_2$: 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}H-NMR δ(DMSO-d_6) 8.62 (s, 1H, C_2-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 $C_{17}H_{12}N_4O_2$: 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}H-NMR δ(CF_3COOH) 9.42 (s, 1H, CHO), 8.75 (d, J=15 Hz, 1H, C_4-H),** 8.43-7.97 (m, 5H, aromatic), 8.02 (d, J=15 Hz, 1H, C_3-H),** 7.70-7.23 (m, 3H, aromatic). Anal. Calcd for $C_{18}H_{11}ClN_4O_2$: 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}H-NMR δ(DMSO-d_6) 12.57 (br, 1H, NH), 11.51 (s, 1H, NH), 8.77 (br, 1H, =$\overset{+}{N}$H-), 8.75 (d, J=15 Hz, 1H, C_4-H),** 7.80 (d, J=7 Hz, 1H, aromatic), 7.55 (d, J=15 Hz, 1H, C_3-H),** 7.73-7.00 (m, 7H, aromatic). Anal. Calcd for $C_{17}H_{13}ClN_4O_2$: 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.

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** determined by decoupling

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