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Asymmetric Transformation. II.[1] Racemization Reaction of 1,4-Benzodiazepinooxazole Derivative

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Optically active crystals of 10-bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydrooxazolo-[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one were obtained by preferential crystallization; they were sometimes levorotatory and sometimes dextrorotatory. This phenomenon was proved to be an example of second-order asymmetric transformation between enantiomers. The rapid racemization reaction, which was essential for asymmetric transformation, was observed in methanol. The decrease of optical rotation obeyed good pseudo first-order kinetics and the half-lives of the racemization in methanol were estimated to be about 21 s at 30 °C, 37 s at 20 °C and 70 s at 10 °C. The mechanism and factors which affect the rate of the racemization are discussed.

Keywords——asymmetric transformation; 1,4-benzodiazepinooxazole; optically active crystal; preferential crystallization; asymmetric transformation; second-order asymmetric transformation; racemization; rate constant

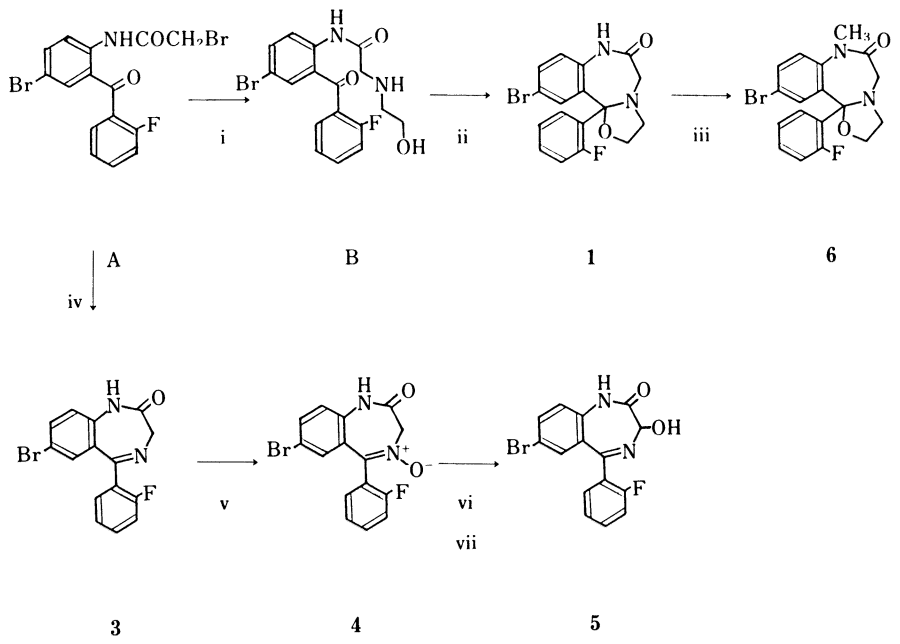
In the course of synthetic studies on 1,4-benzodiazepinooxazole, it was observed that 10-bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (**1**) afforded optically active crystals even though the synthesis was carried out under achiral conditions. Formation of the optically active crystals was proved to take place in the crystallization process of **1**. Moreover, it was also revealed that **1** very rapidly lost its optical activity when dissolved in methanol, which was used as the reaction solvent in the last step of synthesis of **1**. This preferential crystallization seemed to be a special type of second-order asymmetric transformation that occurs in enantiomers.[2] The second-order asymmetric transformation is named for crystallization-induced asymmetric transformation, and usually observed in the case of readily interconvertible diastereomers. However, in the case of enantiomers, this phenomenon is rare, and only a few examples have been reported.[3] We reported our findings in the previous communication.[1] In the present study, we attempted to investigate the properties of **1** in various solvents, and especially the rate of the racemization reaction in methanol, because it is essential for second-order asymmetric transformation that the enantiomers have the property of being racemized easily.

1,4-Benzodiazepinooxazole derivatives (**1**,[4] **6**) and related 1,4-benzodiazepines (**3**,[5] **4**,[6] **5**[7]) were synthesized through the sequence of reactions shown in Chart 1.

Results and Discussion

Ultraviolet (UV) Absorption Spectra of 1

Structural changes of 1,4-benzodiazepinooxazoles in aqueous solution were investigated[8] and the existence of an acid–base equilibrium reaction was confirmed; they were present as benzodiazepinooxazole (**1**) in alkaline solution and as benzodiazepinium ion (**2**) formed by fission of the oxazolidine ring in acidic solution, as illustrated in Chart 2. The equilibrium constant was considered as a kind of acid-dissociation constant, and the pK_a value for **1** was



i: $H_2NCH_2CH_2OH$, ii: MeOH(AcOH)/reflux, iii: CH_3I/NaH, iv: Liq NH_3, v: AcOOH, vi: Ac_2O, vii: NaOH

Chart 1

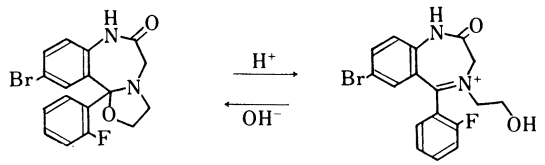


Chart 2. Acid–Base Equilibrium Reaction of Compound **1**

reported to be 6.18.[8a] UV absorption spectra of **1** in methanol, acidic methanol (pH 1—2) and alkaline methanol (pH 10—11) were measured. The spectral change in acidic methanol is shown in Fig. 1. The UV absorption spectra of **1** in methanol and in alkaline methanol showed identical absorption maxima and extinction coefficients (λ_{max} 245 nm, ε 15300). On the other hand, the spectrum in acidic methanol showed similar changes in its absorption maximum and extinction coefficient (λ_{max} 240 nm, ε 35800) to those in aqueous acidic solution. For the confirmation of the benzodiazepinium ion structure in acidic methanol, the UV absorption spectra of **3**, **4** and **5** were compared with that of **1** in acidic methanol. As shown in Fig. 2, compound **4** which has a benzodiazepinium ion structure, showed the most characteristic absorption spectrum among the analogs. These data show that **1** takes the form of the oxazolidine ring-cleaved iminium structure in acidic methanol but takes the ring-closed form in neutral and alkaline methanol.

Racemization of 1

When changes in the optical rotation of **1** were measured in various solvents, the rate of the racemization was much faster in alcohols and slower in chloroform, acetone and dioxane. Half-lives were roughly estimated from experiments carried out at room temperature, and

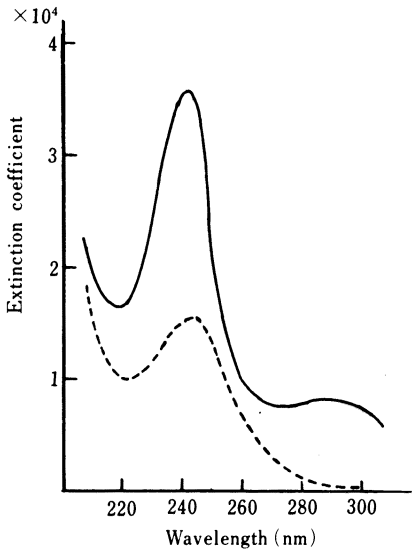


Fig. 1. UV Absorption Spectra of **1** in MeOH at pH 2 and pH 10

——, pH 2; ------, pH 10.

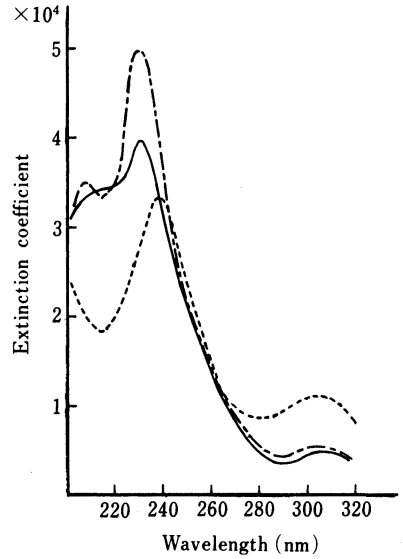


Fig. 2. UV Absorption Spectra of **3**, **4** and **5** in MeOH

——, compound **3**; ------, compound **4**; – – –, compound **5**.

were less than several minutes in methanol and ethanol, several hours in chloroform, about 10 h in acetone and about 1 d in dioxane.

For the second-order asymmetric transformation, faster racemization is more desirable, though the key point is the relative velocity between racemization and formation of crystals. Thus, it was important to estimate the rate of the racemization of **1** in methanol; actually, the racemization seemed to proceed so fast that the test solution completely lost its optical rotation during preparation.

Thus, mixed solvent systems with methanol and dioxane were examined to measure the optical rotation. The rate constants k_{obs} were determined based on Eq. 1,[9] where α_0 is the initial value of the optical rotation and α_t is a value t min later. k_{obs} represents the rate constant of the interconversion of enantiomers and $2k_{obs}$ represents the rate of the racemization expressed in terms of the decrease of optical rotation.

$$2.303 \log \alpha_0/\alpha_t = 2k_{obs}t \quad (1)$$

Methanol contents in dioxane were fixed at 25, 50 and 75% (v/v) and temperatures of 10, 20 and 30 °C were chosen. The observed rate constants are listed in Table I. A rough linear relationship was found between the solvent ratios and $\log k_{obs}$, as shown in Fig. 3. The k values in methanol at the three temperatures were approximately estimated by extrapolation. The half-lives of the racemization calculated from the k values in methanol were about 70 s at 10 °C, 37 s at 20 °C and 21 s at 30 °C. The activation energy of the racemization in methanol was calculated by means of the Arrhenius equation to be about 10 kcal/mol.

Mechanism of the Racemization

The kinetic studies on the racemization of **1** supported the working hypothesis that the racemization proceeded by isomerization *via* the oxazolidine ring-opened intermediate formed by protonation; therefore, the racemization proceeded faster in protic solvents such as alcohol than in aprotic solvents. Protonation of the 1,4-benzodiazepinooxazole (**1**) or successive cleavage of the oxazolidine ring might be the rate-determining step in the

TABLE I. Rate Constants (k_{obs}) and Activation Energies in MeOH–Dioxane

MeOH–dioxane (v/v %)	k_{obs} (min)			Activation energies (kcal/mol)
Temp (°C)	10	20	30	
25/75	4.2×10^{-4}	1.1×10^{-3}	2.1×10^{-3}	13.7
50/50	5.0×10^{-3}	1.2×10^{-2}	2.4×10^{-2}	13.3
75/25	2.9×10^{-2}	6.0×10^{-2}	1.2×10^{-1}	12.1
100/ 0	3.0×10^{-1} a)	5.7×10^{-1} a)	1.0 a)	10.2

a) The rate constants are the calculated values.

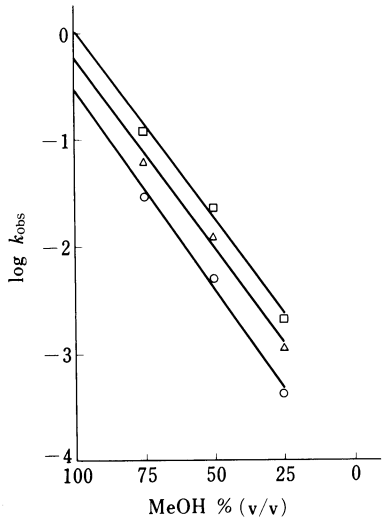


Fig. 3. Effect of MeOH Concentration on the Rate of MeOH Racemization Reaction

○, $\log k_{obs}$ at 10 °C; △, $\log k_{obs}$ at 20 °C; □, $\log k_{obs}$ at 30 °C.

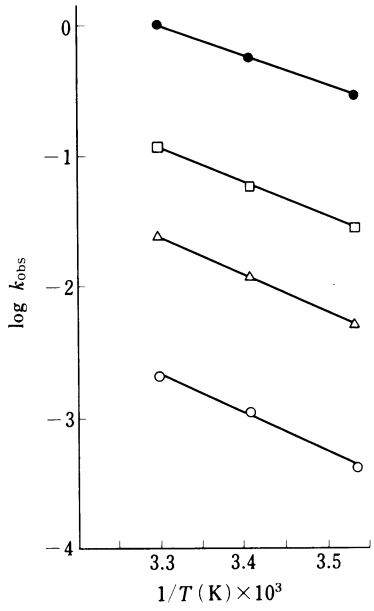


Fig. 4. Arrhenius Plots of the Rate Constants of the Racemization Reaction

○, $\log k_{obs}$ in 25% (v/v) MeOH/dioxane; △, $\log k_{obs}$ in 50% (v/v) MeOH/dioxane; □, $\log k$ in 75% (v/v) MeOH/dioxane; ●, $\log k_{obs}$ in MeOH.

racemization, generating the benzodiazepinium ion (**2**). As UV absorption spectroscopy shows that **1** does not exist as **2** in methanol, the iminium ion (**2**), once produced, generates the racemic form of **1** rapidly by the reverse reaction, because of the stronger acidity of **2** (the pK_a value is 6.18[8a]) than that of methanol (pK_a 16[10a]).

Factors Affecting the Rate of the Racemization

The relationship between acidity or basicity of the solvents and the rate of the racemization of **1** was further studied by measurements of the optical rotation in nitromethane (pK_a 11[10b]), in dioxane containing water (1% and 25%) and in methanol containing triethylamine (1% and 10%). Moreover, the effect of acidity on 1,4-benzodiazepinooxazole was also tested. An optically active *N*-methyl derivative (**6**) was synthesized by methylation of one enantiomer of **1** with methyl iodide. A crystal of **6** obtained showed a large optical rotation, $[\alpha]_D^{25} = -395°$ (dioxane). The rate constants of the racemization under these conditions were determined, as listed in Table II.

TABLE II. Comparison of Rate Constants of **1** and **6** under Various Conditions

Solvent systems	Opt. active comp.	k_{obs}/min (25 °C)	Half life (25 °C)
Nitromethane	**1**	1.3×10^{-1}	2.8 min
1% water/dioxane	**1**	1.3×10^{-4}	45 h
25% water/dioxane	**1**	7.0×10^{-3}	50 min
1% Et_3N/MeOH	**1**	7.5×10^{-2}	4.6 min
10% Et_3N/MeOH	**1**	6.2×10^{-2}	5.6 min
Methanol	**6**	3.0×10^{-3}	116 min

The racemization was clearly accelerated by the presence of protic solvents such as nitromethane and water, but the racemization in nitromethane was slower than that in methanol in spite of the more acidic nature of nitromethane. On the other hand, water acted more effectively than methanol for accelerating the racemization in solvent systems mixed with dioxane of the same ratio.

Addition of triethylamine to a methanol solution of **1** would make the methanol solution basic (pH 10—11), decreasing the rate of the racemization. *N*-Methylation of **1** would be expected to make its benzodiazepinium ion more acidic, as suggested by the pK_a value (4.52) of an analogous *N*-methylated compound.[8a] Therefore, the oxazolidine ring might become somewhat less susceptible to protonation, and the rate of the racemization of **6** would be slower than that of **1**.

Conclusion

The present results suggest that the rate of the racemization of **1** is sufficiently rapid for second-order asymmetric transformation to proceed effectively. Controlled preferential crystallization is practically possible by choosing adequate racemization conditions. Moreover, although 1,4-benzodiazepinooxazoles have been regarded as existing in the form of 1,4-benzodiazepinooxazoles in organic solvents, in fact rapid epimerization always occurred between the enantiomers, especially in methanol and ethanol.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian Associates EM 360L (60 MHz) spectrometer with tetramethylsilane as an internal standard. Infrared (IR) spectra were taken on a JASCO IR-810 spectrometer, and UV spectra were measured on a Hitachi 624 spectrometer. Optical rotation was measured on a Perkin-Elmer 243 polarimeter.

10-Bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (1)——Optically active compound **1** was synthesized from 5-bromo-2-bromoacetamido-2′-fluorobenzophenone[11] by the method reported in the previous communication,[1] to afford crystals, $[\alpha]_D^{25}$ +310° (c=1, dioxane).

7-Bromo-1,3-dihydro-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one (3)——A solution of 5-bromo-2-bromoacetamido-2′-fluorobenzophenone (37.0 g, 89.2 mmol) in 350 ml of liquid ammonia was refluxed for 5 h. The reaction mixture was allowed to stand for the liquid ammonia to evaporate, and the residue was dissolved in 200 ml of water. The precipitate was filtered off and well washed with H_2O. The obtained white powder was added to 600 ml of EtOH and the mixture was refluxed for 6 h. The solution was treated with activated carbon and concentrated under reduced pressure to give crystals of **3** (4.5 g), mp 189—190 °C, (lit.[5] mp 186—187 °C). *Anal.* Calcd for $C_{15}H_{10}BrFN_2O$: C, 54.07; H, 3.03; Br, 23.99; F, 5.70; N, 8.41. Found: C, 54.33; H, 3.03; Br, 23.83; F, 5.70; N, 8.42.

7-Bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide (4)——A solution of 40% peroxyacetic acid (10 ml) was added dropwise to a solution of **3** (10.0 g, 30.0 mmol) in 160 ml of CH_2Cl_2 at 5—7 °C. The mixture was stirred at room temperature for 4.5 h and a crystalline product was precipitated on addition of 600 ml of *n*-hexane. After filtration and washing with *n*-hexane and Et_2O, the product was recrystallized from 380 ml of a mixture of acetone–MeOH (1 : 1) to give **4** (8.48 g, 80.9%), mp 216 °C (dec.). MS m/z (M^+): Calcd for $C_{15}H_{10}BrFN_2O_2$: 347.99094. Found: 347.98790.

7-Bromo-5-(2-fluorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one (5)——A solution of **4** (10.0 g, 28.8 mmol) dissolved in 170 ml of acetic anhydride was kept at 0 °C for 3 h. After concentration of the reaction mixture *in vacuo*, the residue was taken up in CH_2Cl_2 and well washed with water and 1 N NH_4OH solution. The CH_2Cl_2 solution was concentrated and the residue was crystallized on addition of 30 ml of AcOEt to afford 6.5 g of the acetoxy compound, mp 225—227 °C. The acetoxy compound (6.5 g) was suspended in 70 ml of MeOH and 17 ml of 1 N NaOH solution was added dropwise at room temperature. The mixture was stirred at 25 °C for 30 min. 65 ml of H_2O was added to the solution, which was adjusted to pH 4 with AcOH. The resulting crystals were filtered and recrystallized from 110 ml of MeOH to afford **5** (3.3 g), mp 193—194.5 °C (dec.) (lit.[7] mp 196—198 °C). *Anal.* Calcd for $C_{15}H_{10}BrFN_2O$: C, 51.60; H, 2.89; Br, 22.89; F, 5.44; N, 8.02. Found: C, 51.55; H, 2.87; Br, 22.93; F, 5.53; N, 7.99.

10-Bromo-11b-(2-fluorophenyl)-7-methyl-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (6)——Compound **1** (3.77 g, 10 mmol; $[\alpha]_D^{25}$ −309° (*c* = 1, dioxane)) dissolved in 25 ml of anhydrous dimethylformamide (DMF) was added dropwise to a suspension of NaH (net 0.24 g, 10 mmol) in 10 ml of anhydrous DMF. The mixture was stirred at room temperature for 30 min, then 1.56 g of methyl iodide in anhydrous DMF was dropped into the mixture and the whole was stirred at about 5 °C for 2 h. The reaction was quenched with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O and concentrated to give a crystalline residue, which was recrystallized from toluene to afford 1.34 g of colorless crystals, mp 138.5—139.5 °C. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 2.64 (3H, s, N-CH_3), 3.02 (1H, d, J = 11 Hz, 5-H), 3.00—3.50 (2H, m, 2 or 3-H), 3.63 (1H, d, J = 11 Hz, 5-H), 3.78—4.35 (2H, m, 2 or 3-H), 6.69—7.65 (5H, m, Ar-H), 7.70—8.16 (2H, m, Ar-H). $[\alpha]_D^{25}$ −395° (*c* = 1, dioxane).

Measurement of the Rate of Racemization——Measurement in Mixed Solvent: About 250 mg of 1,4-benzodiazepinooxazole was exactly weighed and completely dissolved in a measured amount of dioxane (6.25 ml for 25% (v/v) solution, 12.5 ml for 50%, 18.75 ml for 75%) in a volumetric flask (25 ml) using a hypersonic vibrator. After confirming dissolution of the test sample, the dioxane solution was diluted to 25 ml with MeOH or H_2O. Racemization of the test solution was followed by measuring the decrease in optical rotation at intervals of 5 min with a polarimeter.

Measurement in a Solvent or Et_3N/MeOH: About 250 mg of 1,4-benzodiazepinooxazole was exactly weighed and completely dissolved in a measured amount of solvent or adjusted solvent mixture in a volumetric flask (25 ml), then the solution was diluted to 25 ml with the same solvent or the same solvent mixture. The measurement of the test solution was carried out in the same way as described above.

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9) The rate of the racemization reaction is represented by the following equation as a pseudo first-order reaction: $\ln(a)(a-2x) = 2kt$, where (a) is the initial concentration of **1**, and x is the quantity of one enantiomer converted to the other enantiomer within t min. When the rate of the racemization reaction is calculated from measurements of the optical rotations, the above equation is rearranged by replacing the concentration term with the optical rotation term to give $\ln \alpha_0/\alpha_t = 2kt$.
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