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2-Oxo-1,2,3-oxathiazolidines. Its Application to Separation of Diastereoisomers of β-Amino-alcohols, 6-(4-Methoxy-2-piperidyl)-1,4-dioxaspiro[4,5]decan-6-ol and 2-Hydroxy-2-(2-piperidyl)cyclohexanone

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Recently, Deyrup, *et al.*[2] reported that a variety of β-amino-alcohols were led to 2-oxo-1,2,3-oxathiazolidines by the reaction with thionyl chloride in the presence of tertiary amine. In the previous paper,[3] we reported that 2-oxo-1,2,3-oxathiazolidine derivatives were served for the determination of the stereochemistries of the diastereoisomeric β-amino-alcohols, I and II.

In general, fractional crystallization has been used for separation of diastereoisomeric amino-alcohols, but sometimes with difficulty.[3,4] Now it was found that diastereoisomeric

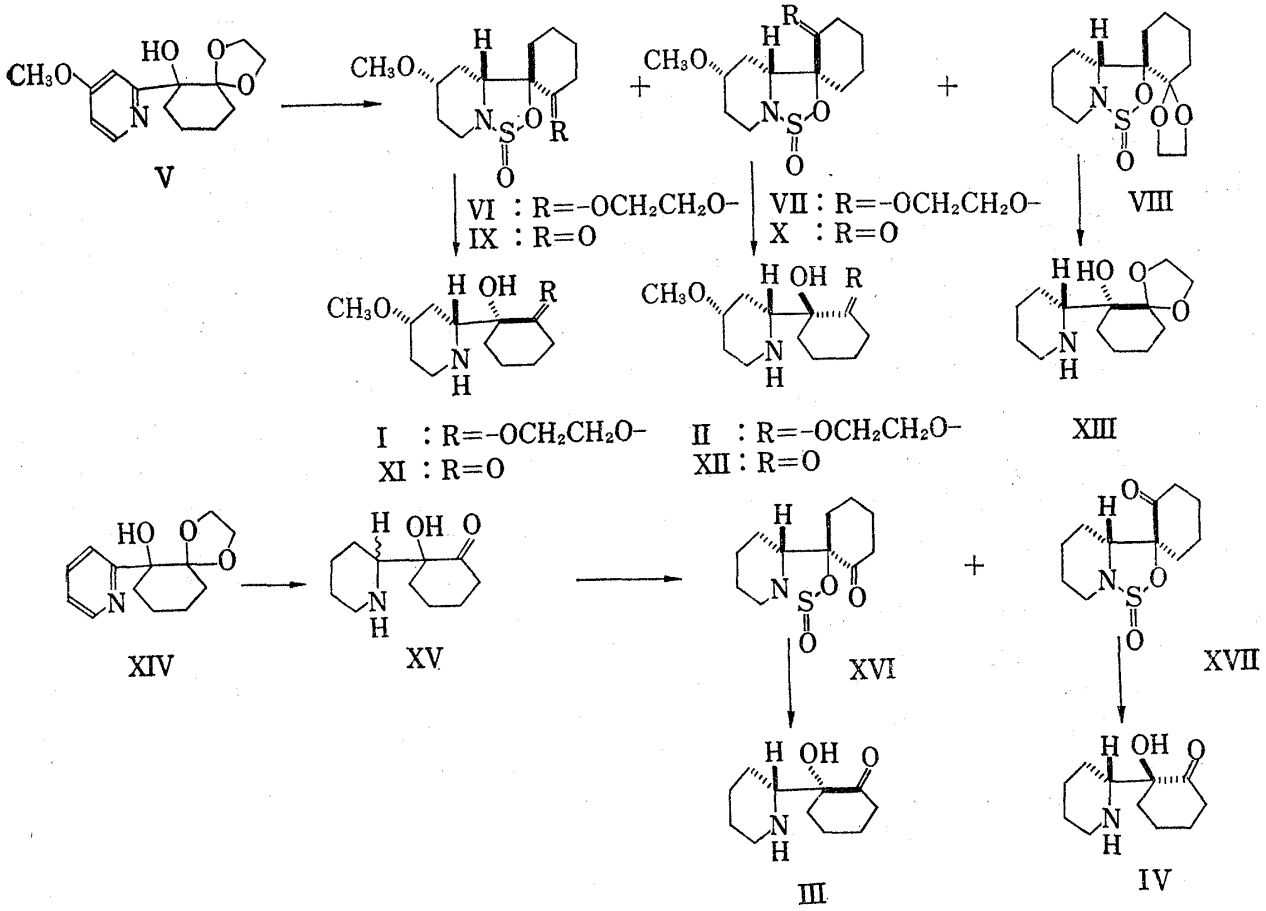

Chart 1

1) Location: *6-1-1, Toneyama, Toyonaka, Osaka.*
2) J.A. Deyrup and C.L. Moyer, *J. Org. Chem.*, 34, 175 (1969).
3) Z. Horii, T. Imanishi, T. Tanaka, I. Mori, M. Hanaoka, and C. Iwata, *Chem. Pharm. Bull.* (Tokyo), 20, 1768 (1972).
4) F.W. Hoover and H.B. Hass, *J. Org. Chem.*, 12, 506 (1947); G. Fodor and J. Kiss, *Nature*, 163, 287 (1949).

2-oxo-1,2,3-oxathazolidines derived from β-amino-alcohols were separated easily by column chromatography.

Though it was reported that 2-oxo-1,2,3-oxathiazolidines were hydrolyzed with hydrochloric acid,[2] the stereochemical aspects of hydrolysis process have not been studied. Accordingly we attempted to examine hydrolysis of 2-oxo-1,2,3-oxathiazolidines, and found that they are easily hydrolyzed with 10% hydrochloric acid at 90° for 30 min or 5% sodium hydroxide in aqueous methanol under reflux for 5 hr to give β-amino-alcohols in excellent yields. Results of the hydrolysis of some oxathiazolidines are summarized in Table I. The products (I, II, XI, and XII) were identical with the corresponding authentic samples,[3] therefore their stereochemistries were completely retained during the hydrolysis.

Table I. Hydrolysis of 2-Oxo-1,2,3-oxathiazolidines (VI, VII, IX and X)

Compound	Method[a]	Product	Yield (%)
VI	A	XI	88
VI	B	I	93
VII	A	XII	81
VII	B	II	87
IX	A	XI	93
X	A	XII	84

a) A: with acid B: with alkali. See Experimental part.

The crude β-amino-alcohols obtained from 6-(4-methoxy-2-pyridyl)-1,4-dioxaspiro[4,5]-decan-6-ol (V)[3] by the hydrogenation over 5% rhodium on alumina in ethanol were reacted with thionyl chloride in benzene in the presence of triethylamine at 0—5° to give the 2-oxo-1,2,3-oxathiazolidines, which were separated by chromatography on silica gel using *n*-hexane–ether (1:1 v/v) and then ether as eluents. The first fraction gave the oxathiazolidine (VIII), the second VI and the third VII, in 4.5%, 54%, and 17% yields, respectively. The products, VI and VII, were identified with the authentic samples[3] and hydrolyzed with alkali to the parent β-amino-alcohols, I and II, respectively. The oxathiazolidine (VIII) was hydrolyzed with alkali to the β-amino-alcohol (XIII).

6-(2-Pyridyl)-1,4-dioxaspiro[4,5]decan-6-ol (XIV)[5] was reduced with sodium-ethanol, followed by hydrolysis with hydrochloric acid to give the piperidine (XV) as an isomeric mixture, which was led to the oxathiazolidines by the reaction with thionyl chloride. Chromatographic separation of the products on silica gel eluted with chloroform gave the diastereoisomers (XVI and XVII) in 58% and 13% yields, respectively. The products, XVI and XVII, were hydrolyzed with acid to the diastereoisomeric β-amino-alcohols, III and IV, respectively. The former was identical with the authentic sample.[6]

Thus we achieved successfully the separation of diastereoisomers of β-amino-alcohols obtained by the reduction of the pyridine alcohols (V and XIV) *via* 2-oxo-1,2,3-oxathiazolidines. As 2-oxo-1,2,3-oxathiazolidines can be easily hydrolyzed with acid or alkali to the parent β-amino-alcohols with the retention of their stereochemistry, they are very useful for separation of diastereoisomers of β-amino-alcohols.

Experimental[7]

Hydrolysis of 2-Oxo-1,2,3-oxathiazolidines. General Methods. A) With Acid——A mixture of the 2-oxo-1,2,3-oxathiazolidine (100 mg) and 10% HCl (5 ml) was heated at 90° for 30 min. After cooling,

5) Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura, S. Saito, N. Shigematsu, K. Kotera, H. Yoshikawa, Y. Sato, H. Nakai, and N. Sugimoto, *Tetrahedron*, **23**, 1165 (1967).
6) Z. Horii, M. Ito, and M. Hanaoka. *Chem. Pharm. Bull.* (Tokyo), **16**, 1754 (1968).

the reaction mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was dried, evaporated and purified to give the β-amino-alcohol.

B) With Alkali——A mixture of the 2-oxo-1,2,3-oxathiazolidine (100 mg), water (1 ml) and 5% NaOH in MeOH (10 ml) was heated under reflux for 5 hr. After removal of the solvent *in vacuo*, the residue was extracted with $CHCl_3$. The extract was washed with water, dried, evaporated and purified to give the β-amino-alcohol. Table I summarized results of the hydrolysis of 2-oxo-1,2,3-oxathiazolidines (VI, VII, IX and X).

Separation of Catalytic Hydrogenation Products of 6-(4-Methoxy-2-pyridyl)-1,4-dioxaspiro[4,5]decan-6-ol (V)——The pyridine (V, 0.50 g) was hydrogenated in ethanol (20 ml) over 5% Rh-Al_2O_3 (0.9 g) at 100° and 100 atm pressure for 30 hr. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. To a stirred solution of the residue (0.49 g) in dry benzene (10 ml) containing Et_3N (0.9 ml) was added a solution of $SOCl_2$ (0.25 ml) in dry benzene (10 ml) dropwise over a period of 30 min under ice–water cooling. The reaction mixture was stirred for 3 hr under cooling and then allowed to stand at room temperature overnight. Inorganic substance was filtered off and the filtrate was washed with 10% HCl (10 ml). The acidic layer was made alkaline with K_2CO_3 and extracted with ether. Evaporation of the dried extract gave 69 mg (14%) of the starting material (V) as colorless plates, mp 57.5—59°. The benzene layer was evaporated to give an oily residue (0.51 g), which was chromatographed on silica gel (16 g). The first fraction eluted with *n*-hexane–ether (1:1 v/v) gave a solid, which was recrystallized from *n*-hexane to give 24 mg (4.5%) of the oxathiazolidine (VIII) as colorless plates, mp 94—95.5°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1154 (SO). *Anal.* Calcd. for $C_{13}H_{21}O_4NS$: C, 54.34; H, 7.37; N, 4.88. Found: C, 54.44; H, 7.34; N, 4.72. Mass Spectrum *m/e*: 287 (M^+), 131, 99, 84. The second fraction eluted with ether gave 320 mg (54%) of the oxathiazolidine (VI) as colorless needles, mp 95—96°. IR ν_{max}^{KBr} cm^{-1}: 1180 (SO). The third fraction eluted with ether gave 100 mg (17%) of the oxathiazolidine (VII) as colorless plates, mp 117—118°. IR ν_{max}^{KBr} cm^{-1}: 1170 (SO). These products (VI and VII) were identified with the authentic samples[3] by mixed mp and comparison of IR.

The oxathiazolidine (VIII, 45 mg) was hydrolyzed according to general method B. The crude product was recrystallized from acetone to give 28 mg (75%) of the β-amino-alcohol (XIII) as colorless needles, mp 151—152°. IR ν_{max}^{KBr} cm^{-1}: 3335, 3180 (OH, NH). *Anal.* Calcd. for $C_{13}H_{23}O_3N$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.65; H, 9.58; N, 5.62.

Separation of Reduction Products of 6-(2-Pyridyl)-1,4-dioxaspiro[4,5]decan-6-ol (XIV)——To a stirred solution of the pyridine (XIV, 1.0 g) in boiling abs. EtOH (60 ml) was added Na (10 g) portionwise over a period of 1 hr. The reaction mixture was stirred for 3 hr under reflux, then neutrallized with conc. HCl under cooling and extracted with $CHCl_3$. The extract was dried and evaporated. A solution of the residue in 10% HCl (20 ml) was heated at 90° for 3 hr. After cooling, the mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was dried and evaporated to give an oily residue (720 mg). To a stirred solution of the residue in dry benzene (50 ml) containing Et_3N (1.8 ml) was added a solution of $SOCl_2$ (0.5 ml) in dry benzene (20 ml) dropwise over a period of 30 min under ice–water cooling. The reaction mixture was stirred for 3 hr under cooling and then allowed to stand at room temperature overnight. Inorganic substance was filtered off and the filtrate was washed with water, 10% HCl and water, and dried. Evaporation of the solvent gave an oily residue (0.85 g), which was chromatographed on silica gel (20 g) using $CHCl_3$ as a eluent. The first fraction gave a solid, which was recrystallized from *n*-hexane to give 0.60 g (58%) of the oxathiazolidine (XVI) as colorless needles, mp 123—124°. IR ν_{max}^{KBr} cm^{-1}: 1723 (CO), 1152 (SO). *Anal.* Calcd. for $C_{11}H_{17}O_3NS$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.35; H, 7.02; N, 5.61. Mass Spectrum *m/e*: 243 (M^+), 131. The second fraction gave a solid, which was recrystallized from *n*-hexane to give 0.13 g (13%) of the oxathiazolidine (XVII) as colorless plates, mp 144—145°. IR ν_{max}^{KBr} cm^{-1}: 1724 (CO), 1154 (SO). *Anal.* Calcd. for $C_{11}H_{17}O_3NS$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.60; H, 7.04; N, 5.49. NMR τ: 6.12 (1H, d of d, $J=2$ and 10 cps, C_2,-H).[8] Mass Spectrum *m/e*: 243 (M^+), 131.

The oxathiazolidine (XVI, 250 mg) was hydrolyzed according to general method A. The crude product was recrystallized from petr. ether (bp~50°) to give 195 mg (95%) of the β-amino-alcohol (III) as colorless plates, mp 89—91°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3475, 3312 (OH, NH), 1716 (CO). The product (III) was identified with the authentic sample[6] by mixed mp and comparison of IR.

The oxathiazolidine (XVII, 80 mg) was hydrolyzed according to general method A. The crude product was recrystallized from petr. ether (bp~50°) to give 55 mg (85%) of the β-amino-alcohol (IV) as colorless plates, mp 39—40°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3438, 3310 (OH, NH), 1716 (CO). *Anal.* Calcd. for $C_{11}H_{19}O_2N$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.42; H, 9.46; N, 6.87.

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7) All melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken on Hitachi Perkin-Elmer H-60 type spectrometer at 60 Mc in $CDCl_3$ with $(CH_3)_4Si$ as an internal standard. Mass spectra were taken on Hitachi RMU-60 spectrometer at 70 eV. Silica gel (Mallinckrodt) was used for column chromatography. Organic extracts were dried over anhydrous $MgSO_4$.

8) The corresponding signal does not appear in the lower region than 6.4 τ in XVI. In XVII the C_2,-H was deshielded by the carbonyl at C_1 but not in XVI. These data supported the stereochemistries of XVI and XVII.[3]