

Studies on Hydroxy Amino Acids. I. A New Synthesis of Aziridine Derivative from β -Hydroxy α -Amino Acid

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N-Tosyl-3-methyl-2-aziridinecarboxylic acid anilide was obtained by the β -elimination reaction of *N,O*-ditosyl-L-threonine anilide. The ethyleneimine ring of this compound was readily cleaved by acetic acid in the presence of boron trifluoride and *N*-tosyl-*O*-acetyl-L-threonine anilide was obtained. Formaldehyde also reacted with this compound in the presence of the same catalyst and gave 1,3-oxazolidine and 1,3-oxazine derivatives.

We have been studying the synthesis of α,β -unsaturated α -amino acid derivatives by dehydration of β -hydroxy- α -amino acid derivatives and have observed the formation of *N*-acyl- α,β -unsaturated amino acid esters from the corresponding *N*-acyl- β -hydroxyamino acid esters as described by Photaki.¹⁾

However, in the case of *N,O*-ditosyl-L-threonine anilide, an unexpected product, *N*-tosyl-3-methyl-2-aziridinecarboxylic acid anilide, was obtained in good yield.

Among the reports concerning the synthesis of aziridinecarboxylic acid derivatives,²⁻⁶⁾ only Smrt⁷⁾ has reported findings similar to the above. In his study he asserted that the aziridinecarboxylic acid ester was produced when *N*-trityl-*O*-mesylserine methyl ester in the benzene solution was treated with *N*-ethyl-piperidine.

We have also found that the ethyleneimine ring of our aziridine derivative is readily cleaved by acetic acid or formaldehyde in the presence of boron trifluoride. Acetic acid gave *N*-tosyl-*O*-acetyl-L-threonine anilide and formaldehyde gave 3-tosyl-5-methyl-1,3-oxazolidine-4-carboxylic acid anilide (IVA) and 3-phenyl-4-oxo-5-tosylamino-6-methyl-1,3-tetrahydro-oxazine (IVB) as shown in Fig. 1.

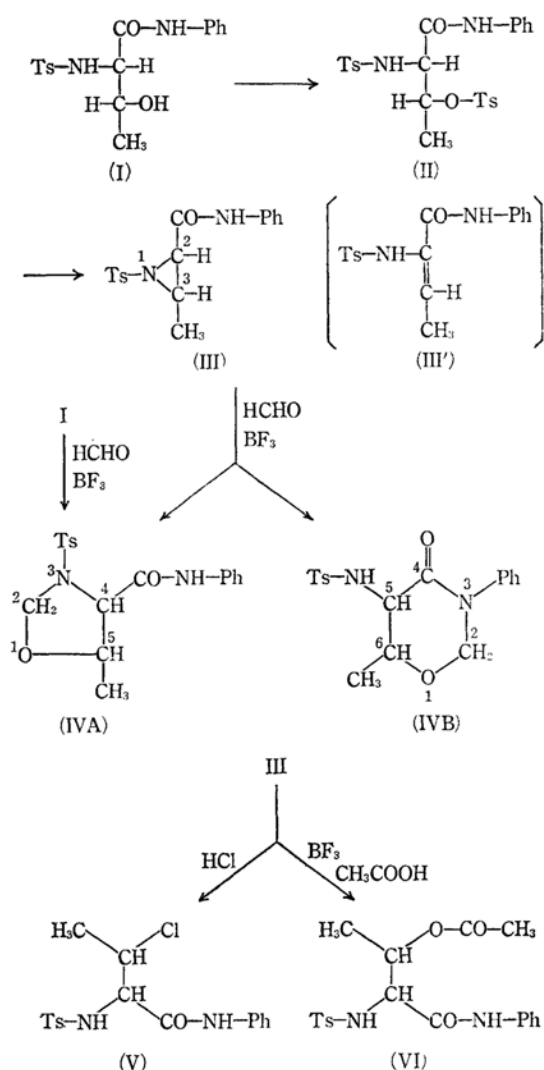


Fig. 1.

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The compound II in dry tetrahydrofuran was treated with an equivalent amount of diethylamine to produce III. The elemental analysis and the molecular weight of III showed the molecular formula $C_{17}H_{18}O_3N_2S$. From this results, it was suggested that the compound is a dehydration product of I and has a structure of either III or III'. But III was confirmed by the spectral data.

The infrared spectrum indicated the presence of secondary amide bands at 1675 cm^{-1} and 1523 cm^{-1} respectively. But the characteristic absorption of a trisubstituted vinyl double bond was not detected. However, a new absorption band appeared at 885 cm^{-1} , this may be attributed to the aziridine ring deformation.

The NMR spectrum also supported the structure III. The vinyl proton and tosylated amide proton were not detected in the corresponding regions. The NMR spectrum of III showed one-proton octet at δ 3.12 ppm with $J=7.7$ cps for the C_3 -proton, one-proton doublet at δ 3.47 ppm with $J=7.7$ cps for the C_2 -proton, $J_{2,3}=7.7$ cps (*cis*-position).⁸⁾

The ethyleneimine ring of III is readily cleaved by hydrochloric acid or toluenesulfonic acid, and V and II were obtained respectively. However, acetic acid cannot react with III but reacted with it in the presence of boron trifluoride-etherate and IV was obtained.

In the presence of the same catalyst, III also reacted with paraformaldehyde at 45°C and the products, IVA and IVB were separated by silica gel chromatography in the yield of 45% and 5% respectively. From the elemental analyses and the molecular weights, IVA and IVB were shown to have the same molecular formula of $C_{18}H_{20}O_4N_2S$ which indicated just one formaldehyde molecule combined with III.

Proof for the structure IVA was obtained by the spectral data and the direct synthesis of IVA from I and formaldehyde.

The infrared absorption spectrum of IVA shows secondary amide bands at 1685 cm^{-1} and 1525 cm^{-1} respectively and the characteristic strong bands of $-N-C-O-$ group in a ring structure at 1155 , 1110 , 1087 and 1073 cm^{-1} .⁹⁾

The NMR spectrum of IVA showed a three-proton doublet at δ 1.05 ppm with $J=5.8$ cps for the C_5 -methyl protons, one-proton doublet at δ 3.64 ppm with $J=6.8$ cps for the C_4 -proton, one-proton octet at δ 4.17 ppm with $J=5.8$ and 6.8 cps for the C_6 -proton, two one-proton doublets at δ 4.62 and 5.34 ppm for the AB type C_2 -methylene protons, and no tosylated amide proton was detected in the corresponding region.

The final structure IVB was determined by the

spectral data.

The infrared absorption spectrum of IVB indicated the presence of a carbonyl group in tertiary amide bond at 1695 cm^{-1} and also showed a $-N-C-O-$ group in a ring structure at 1145 , 1112 , 1087 and 1050 cm^{-1} .⁹⁾

The NMR spectrum of IVB showed a three-proton doublet at δ 1.19 ppm with $J=6.8$ cps for the C_6 -methyl protons, one-proton quartet at δ 4.20 ppm with $J=2.0$ and 3.3 cps for the C_5 -proton, one proton octet at δ 3.86 ppm with $J=3.3$ and 6.8 cps for the C_6 -proton, two-proton doublet at δ 5.39 ppm for the C_2 -methylene protons and one proton doublet at δ 5.58 ppm with $J=2.0$ cps for the tosylated amide proton. The mono-substituted amide proton was not detected in the corresponding region.

Experimental

All melting points are uncorrected. NMR spectra were obtained with a Varian A-60 spectrometer in $CDCl_3$ solution and chemical shifts are given from TMS as an internal reference. Infrared spectra were recorded with a JASCO-DS-402G (Japan Spectroscopic Co., Ltd.).

N-Tosyl-L-threonine Anilide (I). Dicyclohexylcarbodiimide (30.9 g, 0.15 mol) in methylene chloride (80 ml) was added drop by drop to the mixture of *N*-tosyl-L-threonine (30.9 g, 0.1 mol) and aniline (9.3 g, 0.1 mol) in methylene chloride (800 ml) with stirring at 0°C . After adding the solution, the stirring was continued for one hour at 0°C and the reaction mixture was allowed to stand at room temperature for 4 hr. The urea produced was filtered off and the filtrate was allowed to stand in a refrigerator. The separated crystals were collected and recrystallized from tetrahydrofuran-*n*-hexane. The total yield was 26.9 g (70%), mp $145-146^\circ\text{C}$; $[\alpha]_D^{25} -37.21^\circ$ (c 1.13, dioxane).

Found: C, 58.48; H, 5.77; N, 8.10%. Calcd for $C_{17}H_{20}O_4N_2S$: C, 58.60; H, 5.79; N, 8.04%.

N,O-Ditosyl-L-threonine Anilide (II). *p*-Toluenesulfonyl chloride (38.0 g, 0.2 mol) in pyridine (60 ml) was added drop by drop to a solution of I (38.4 g, 0.1 mol) in pyridine (200 ml) with stirring at 0°C . After stirring for thirty minutes, the reaction mixture was allowed to stand at room temperature for 4 hr.

Ice water was added to the reaction mixture until it became turbid and the mixture was kept in a refrigerator overnight. The separated crystals were filtered and washed with ethanol. Recrystallization from tetrahydrofuran-*n*-hexane gave fine crystals. The total yield was 29.6 g (65%), mp $186-188^\circ\text{C}$; $[\alpha]_D^{25} -16.11^\circ$ (c 1.21, CH_2Cl_2).

Found: C, 57.70; H, 5.27; N, 5.63; S, 12.32%. Calcd for $C_{24}H_{26}O_6N_2S_2$: C, 57.35; H, 5.21; N, 5.57; S, 12.73%.

N-Tosyl-3-methyl-2-aziridinecarboxylic Acid Anilide (III). Diethylamine (1.02 ml, 0.01 mol) was added to a solution of II (5.02 g, 0.01 mol) in tetrahydrofuran (50 ml). After incubation at 37°C for 5 hr, the reaction mixture was diluted with ether until it became turbid. The diethylamine *p*-toluenesulfonate produced was filtered off and from the filtrate solvent

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was removed under reduced pressure. The resultant material was dissolved in ether under warming, insoluble material was filtered off and the filtrate was allowed to stand in a refrigerator. White needle crystals were obtained. The yield was 2.15 g (65%). The melting point was different depending upon the solvent of recrystallization: mp 50–56°C for ether, 90–91°C for ethanol-water. $[\alpha]_D^{20}$ –65.3° (c 1.08, EtOH), $\lambda_{max}^{MeOH-H_2O}$ 246 m μ (ϵ =13000), ν_{max}^{KBr} 1675 (amide I), 1523 (amide II) and 885 cm $^{-1}$ (aziridine ring).

Found: C, 61.97; H, 5.61; N, 8.21; S, 9.54%; mol wt (Rast), 315 \pm 15. Calcd for C₁₇H₁₈O₃N₂S: C, 61.80; H, 5.49; N, 8.48; S, 9.70%; mol wt, 330.4.

NMR: δ 1.33 ppm (3H (d), J =5.8 cps, C₃-methyl proton); 3.12 ppm (1H (d) J =5.8, J =7.7 cps, C₂-proton) 3.47 ppm (1H (d) J =7.7 cps, C₂-proton)

3-Tosyl-5-methyl-1,3-oxazolidine-4-carboxylic Acid Anilide (IVA).

3-Phenyl-4-oxo-5-tosylamino-6-methyl-1,3-tetrahydrooxazine (IVB). Paraformaldehyde (1.8 g, 0.02 mol) and ten drops of boron trifluoride etherate (47%) were added to the solution of III (6.60 g, 0.02 mol) in chloroform (50 ml) and stirred at 45°C for 50 hr.

Unreacted paraformaldehyde was filtered off and the solvent was removed. The oily residue (8.5 g) was chromatographed on silica gel (150 g) with benzene-ethyl acetate (10 : 1, v/v) to yield two reaction products.

From the fraction of R_f 0.74 on silica gel thin-layer chromatography with benzene-ethyl acetate (10 : 1, v/v) was obtained a product IVA yield 3.25 g (45%), mp 36–38°C from ether-petroleum ether; $[\alpha]_D^{20}$ –215.5°

(c 1, EtOH), $\nu_{max}^{CCl_4}$ 1685 (amide I), 1525 (amide II), 1115, 1110, 1087 and 1073 cm $^{-1}$ (–N–C–O– ring).

Found: C, 59.28; H, 5.79; N, 7.64; S, 9.27%; mol wt, 350 \pm 10 (Rast). Calcd for C₁₈H₂₀O₄N₂S: C, 59.98; H, 5.59; N, 7.77; S, 8.90%; mol wt, 360.

NMR: δ 1.05 ppm (3H (d) J =5.8 cps, C₅ methyl proton); 3.64 ppm (1H (d) J =6.8, C₄ proton); 4.17 ppm (1H (o) J =5.8, J =6.8, C₅ proton); 4.62, 5.34 ppm (2H (d) C₂ methylene proton)

From the fraction of R_f 0.44 (on the same silica gel thin-layer chromatography) was obtained a product IVB, 0.35 g (5%) mp 137–137.5°C (from ethyl acetate-ether); $[\alpha]_D^{20}$ +35.6° (c 1, EtOH), ν_{max}^{KBr} 1145, 1112, 1087 and 1060 (–N–C–O– ring), 3250 cm $^{-1}$ (Tos-NH–).

Found: C, 60.04; H, 5.60; N, 7.71; S, 8.59%; mol wt, 355 \pm 10 (Rast). Calcd for C₁₈H₂₀O₄N₂S: C, 59.98; H, 5.59; N, 7.77; S, 8.90%; mol wt, 360.

NMR: 1.19 ppm (3H (d) J =6.8 cps, C₆ methyl proton); 3.86 ppm (1H (o) J =3.2, 6.8 cps, C₆ proton); 4.86 ppm (1H (q) J =2.0, 3.2 cps, C₅ proton); 5.39 ppm (2H (d) C₂ methylene proton); 5.58 ppm (1H (d) J =2.0 cps, tosylated amide proton)

From the fraction of R_f 0.66 on the same silica gel thin-layer chromatography 0.32 g of unreacted starting material was recovered.

3-Tosyl-5-methyl-1,3-oxazolidine-4-carboxylic Acid Anilide (IVA) from *N*-Tosyl-L-threonine Anilide (I).

Five drops of boron trifluoride etherate (47%) were added to a mixture of I (1.74 g, 0.005 mol) and paraformaldehyde (0.9 g) in acetic acid (10 ml) and the mixture was stirred at 85°C for 20 min, and the solvent was evaporated under reduced pressure. The residual oily substance was dissolved in ether and was washed with 1 N sodium bicarbonate and water to remove a trace amount of acetic acid and aldehyde. The ether solution was dried over anhydrous sodium sulfate and the solvent was removed. Colorless oil (1.75 g) obtained gradually solidified to a glassy mass mp 36–38°C, R_f 0.74 (on silica gel thin-layer chromatography with benzene-ethyl acetate (10 : 1, v/v). This compound was identified with IVA by the IR spectrum and R_f value on silica gel thin-layer chromatography.

N-Tosyl- α -amino- β -chloro-*n*-butyric Acid Anilide (V).

Compound III (0.33 g, 1mmol) was warmed to be dissolved in 2 N hydrochloric acid (2 ml). The solution was kept at 40°C for 2 hr, and fine crystals gradually appeared during this period. The crystals were filtered and collected with theoretical yield. Recrystallization from methanol-water gave pure materials, mp 163–164°C, $[\alpha]_D^{20}$ –51.13° (c 1.02, MeOH).

Found: C, 55.70; H, 5.62; N, 7.63; S, 8.87; Cl, 9.66%. Calcd for C₁₇H₁₉O₃N₂ClS: C, 55.66; H, 5.22; N, 7.64; S, 8.74; Cl, 9.66%.

N-Tosyl-*O*-acetyl-L-threonine Anilide (VI).

A mixture of III (1.98 g, 0.006 mol), acetic acid (6 ml), and five drops of boron trifluoride etherate (47%) was stirred at 45°C for 4 hr. The reaction mixture was dissolved in ethyl acetate (100 ml) and was washed with 1 N sodium carbonate and then with 1 N sodium bicarbonate and water. The organic layer was dried over anhydrous sodium sulfate. After removal of the solvent, the crystalline residue was recrystallized from ethyl acetate-*n*-hexane to give a substance, mp 173–173.5°C in 88% yield. This substance was found to be identical with the authentic sample*¹ (*N*-tosyl-*O*-acetyl-L-threonine anilide) by the IR spectrum and the mixed melting point test.

$[\alpha]_D^{20}$ –1.82° (c 1.92, dioxane), ν_{max}^{Nujol} 1736 (–OAc), 1661 (amide I) and 1534 cm $^{-1}$ (amide II).

Found: C, 58.62; H, 5.78; N, 7.25; S, 8.23%. Calcd for C₁₉H₂₂O₅N₂S: C, 58.45; H, 5.68; N, 7.17; S, 8.21%.

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*¹ This sample was prepared from *N*-Tosyl-L-threonine anilide (I) and acetic anhydride in dry pyridine.