CHEMISTRY LETTERS, pp. 591-594, 1975. Published by the Chemical Society of Japan

STUDIES ON HYDROXY AMINO ACIDS V. SYNTHESIS AND N-ACYLATION OF 3-METHYL-L-AZYLYLGLYCINE BENZYL ESTER [1)]

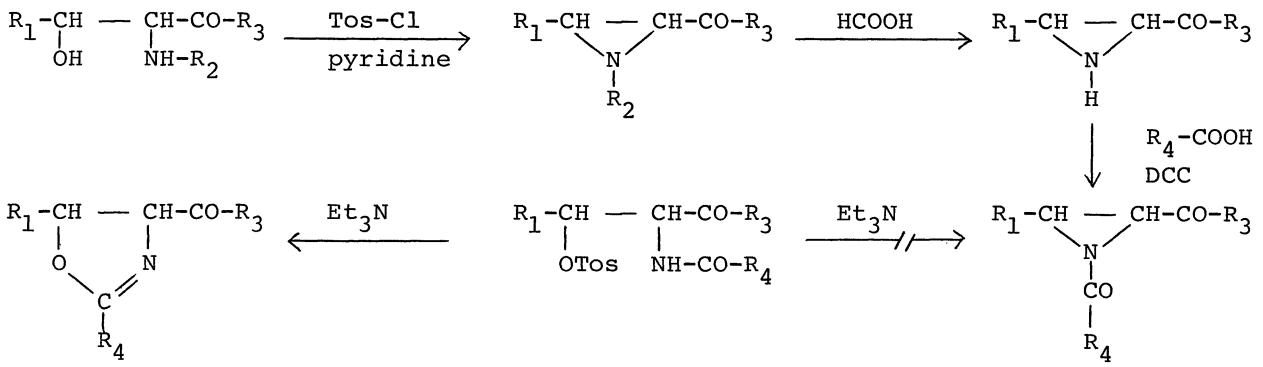
Kenji OKAWA, Kiichiro NAKAJIMA, Takumi TANAKA, and Yuriko KAWANA
Department of Chemistry, Faculty of Science, Kwansei Gakuin University, Nishinomiya 662

Optically active 3-methyl-L-aziridinecarbonyl glycine ester was successfully obtained from the corresponding N-trityl derivative by the careful treatment with formic acid and Z-Gly-3-Me-L-Azy-Gly-OBzl was also prepared without cleavage of aziridine ring by the usual DCC method.

It is a well known fact that the β-elimination reaction of the hydroxy groups of the N-alkyl- or N-tosyl-β-hydroxy amino acid derivatives give the corresponding aziridine carboxylic acid derivatives as described by J.Smrt[2)] and K.Okawa[1),3)]. In the case of the N-acylated hydroxy amino acid ester derivatives and N-carbobenzoxy derivatives, α,β-unsaturated dehydroalanine derivatives were usually obtained by the above reaction. On the other hand, D.Elliott[4)] and A.Wagner[5)] reported that the oxazoline derivatives were obtained by the same procedure from the N-benzoyl-threonine methyl ester or N-benzoyl-β-nitrophenylserine ethyl ester.

In the previous paper, the authors reported that the aziridine carboxylic acid peptides were obtained from the corresponding N-aminoacyl-L-threonylglycine derivatives, however, the conclusive evidence of the structure could not be obtained, because of the color reaction of aziridine ring[6)] was not detected, and the relatively higher values (4.49, 4.80ppm) as to aziridine ring proton shift were recorded in NMR spectrum.

In the present paper, the authors succeeded the synthesis of N-terminus free aziridine carboxylic acid peptide from the N-Tri-L-Thr-Gly-OBzl by using of formic acid at 0°C, and Z-Gly-3-Me-L-Azy-Gly-OBzl was obtained as the authentic sample



R_1:CH_3; R_2:Tri; R_3:Gly-OBzl; R_4-CO-:Z-Gly-

Fig.1 β-ellimination products of hydroxy amino acid derivative.

by the direct acylation of 3-Me-L-Azy-Gly-OBzl with the aid of N,N'-dicyclohexylcarbodiimide as shown in Fig. 1.

Consequently, it was concluded that the compound previously reported[1] which was prepared by the β-ellimination reaction from Z-Gly-O-Tos-L-Thr-Gly-OBzl is oxazoline but not aziridine derivative. And at the same time, N-phenacyl and N-Z-phenylglycyl-aziridinecarbonylglycine ester derivatives were also prepared by the above procedure and was confirmed as follows. That is, all of the compounds Z-Gly-3-Me-L-Azy-Gly-OBzl, Phenacyl-3-Me-L-Azy-Gly-OBzl, and Z-D-PhGly-3-Me-L-Azy-Gly-OBzl shows positive aziridine test and the values of proton magnetic resonance to give the chemical shifts around 2.1-2.8ppm(α proton) and 3.0-3.3ppm(β proton) from the tetramethylsilane as a standard. From the above results, it was confirmed that the aziridine ring is retained. In the case of Phenacyl-3-Me-L-Azy-Gly-OBzl, the characteristic absorption of N-carbonyl group attached to the aziridine ring was recorded at 1705 cm^{-1}.

Experimental

Boc-L-Thr-Gly-OBzl (I)

Boc-L-Thr-OH(22.0g, 0.1mol) was coupled with H-Gly-OBzl(from the p-toluensulfonate 37.2g, 0.11mol) by the aid of DCC(22.7g, 0.12mol) and N-hydroxybenztriazol(16.2g, 0.12mol) in methylenechloride at -10°C. Yield 32.0g(95.2%), mp 62-4°C, $[\alpha]_D^{23}$+32.0° (c=1.0, MeOH), Anal Found: C, 59.16 ; H, 7.25; N, 7.66%. Calcd for $C_{18}H_{26}O_6N_2$: C, 59.00; H, 7.15; N, 7.65%.

H-L-Thr-Gly-OBzl (II)·HCl

To a solution of I(20.2g, 60mmol) in ethylacetate containing anisole(1 ml), was bubbled dry hydrogen chloride at 0°C for 30 min. After the solvent was evaporated under reduced pressure, anhydrous ether was added to the residual products. II·HCl was collected by filtration in the theoretical yield. It was immediately used for the next reaction.

Tri-L-Thr-Gly-OBzl (III)

To a solution of II(16.1g, 59mmol) in $CHCl_3$ containing Et_3N(25ml, 0.18mol) at -5°C, was added drop by drop a solution of tritylchloride(19.8g, 71mmol) in $CHCl_3$ with stirring for 1hr. After the reaction mixture was allowed to stand overnight, the solution was washed with 5% tartaric acid and water, and was dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure. The residual oil was crystallized from ether-n-hexane. Yield 22.8g(71.7%), mp 136.5-8°C, $[\alpha]_D^{23}$ -54.0°(c=1.0, $CHCl_3$), Anal Found: C, 75.88; H, 6.37; N, 5.30%. Calcd for $C_{32}H_{32}O_4N_2$: C, 75.57; H, 6.34; N, 5.51%.

Tri-3-Me-L-Azy-Gly-OBzl (IV)

To a solution of III(16.5g, 32.4mmol) in anhydrous pyridine(50ml), was added drop by drop a pyridine solution of p-tosylchloride(18.5g, 97.2mmol) in ice-salt bath with stirring. After the addition was over, the reaction mixture was allowed to stand in a refrigerator at -10°C for 3 day, and was concentrated under reduced pressure. The residual product was dissolved in ethylacetate and washed with water and the organic layer was dried over anhydrous sodium sulfate. After the solution was evaporated under reduced pressure, the residual oil was crystallized from ethylacetate-n-hexane. Yield 13.6g(88.3%), mp 175.0-6.5°C, $[\alpha]_D^{23}$-70.4°(c=1.3, DMF).

IV was detected by the positive aziridine test[6]. In this procedure, the aziridine derivative was directly obtained without isolation of O-tosyl derivative. NMR($CDCl_3$); δ:1.31ppm(3H d,5.0Hz, $C\underline{H}_3$-CH-), 1.62ppm(1H m β-proton), 2.04ppm(1H d, 6.2Hz(cis), α-proton), 4.18ppm(2H d, 5.8Hz, -NH-$C\underline{H}_2$-), 5.19ppm(2H s C_6H_5-$C\underline{H}_2$-). Anal Found: C, 78.74; H, 6.34; N, 5.88%. Calcd for $C_{32}H_{30}O_3N_2$: C, 78.34; H, 6.16; N, 5.71%.

H-3-Me-L-Azy-Gly-OBzl (V)

To a mixed solution of IV(4.76g, 10mmol) in $CHCl_3$(15ml) and absolute methanol (20ml) in ice bath, was added drop by drop formic acid(20ml). After the reaction mixture was stirred for 3 day at same temperature, it was concentrated under reduced pressure at 0°C. The appeared crystals were filtered off and were washed with methanol. The crystals were tritylmethylether(mp 82-84°C)[7], which was identified by NMR. The mother solution was concentrated under reduced pressure, the obtained oil was dissolved in ethylacetate. After the solution was washed with M sodium bicarbonate and water, the solution was dried over anhydrous sodium sulfate, and was concentrated under reduced pressure, the residual product was crystallized from ethylacetate-ether-n-hexane. Yield 1.85g(74.1%), mp 54-55°C, $[\alpha]_D^{23}$-44.0°(c=1.0, MeOH). V was detected by the positive aziridine test[6]. NMR($CDCl_3$):δ:1.16ppm(3H d, 5.8Hz, $C\underline{H}_3$-CH-); 2.35ppm(1H m, β-proton); 2.70ppm(1H d, 6.8Hz(cis), α-proton); 1.21ppm(1H s,$\underline{H}$-N-(aziridine)); 4.06ppm(2H d, 5.6Hz, -NH-$C\underline{H}_2$-); 5.15ppm(2H s, C_6H_5-$C\underline{H}_2$-); 6.70ppm(1H b -N$\underline{H}$-CH_2-); 7.31ppm(5H s, $C_6\underline{H}_5$-CH_2-). Anal Found: C, 62.74; H, 6.64; N, 11.34%. Calcd for $C_{13}H_{16}O_3N_2$: C, 62.89; H, 6.50; N, 11.28%.

Z-Gly-3-Me-L-Azy-Gly-OBzl (VI_a)

A solution of DCC(227mg, 1.1mmol) in $CHCl_3$ was added drop by drop into a solution of V(248mg, 1mmol) and Z-Gly-OH(209mg, 1mmol) in $CHCl_3$ at 0°C with stirring. After the reaction mixture was allowed to stand overnight in a refrigerator, the appeared DCurea was filtered off. The mothor solution was washed with 5% tartaric acid, M sodium bicarbonate and water successively, and was dried over anhydrous sodium sulfate. After the solution was concentrated under reduced pressure, the residual product was crystallized from ethylacetate-ether-n-hexane. Yield 381mg (89.0%), mp 123.5 -4.5°C, $[\alpha]_D^{23}$-58.2°(c=1.0, EtOAc). VI_a was detected by the positive aziridine test[6]. NMR($CDCl_3$):δ: 1.28ppm(3H d, 5.5Hz, $C\underline{H}_3$-CH-); 2.80ppm(1H m, β-proton); 3.22ppm(1H, d, 6.8Hz(cis), -proton); 3.98ppm(2H d, 5.6Hz, -NH-$C\underline{H}_2$-); 3.80, 4.22ppm(2H 2q, 6.2,18Hz, 5.2,18Hz, -NH-$C\underline{H}_2$-); 5.05, 5.11ppm(4H,2s, C_6H_5-$C\underline{H}_2$-CO, C_6H_5-$C\underline{H}_2$-O); 5.50ppm(1H b, -N$\underline{H}$-CH_2-CO_2); 6.72ppm(1H b, -N$\underline{H}$-CH_2-CO-). Anal Found: C, 62.88; H, 5.70; N, 9.68%. Calcd for $C_{23}H_{25}O_6N_3$: C, 62.86; H, 5.73; N, 9.56%.

Phenacyl-3-Me-L-Azy-Gly-OBzl (VI_b)

Phenylacetic acid(136mg, 1mmol) was coupled with V(248mg, 1mmol) by the aid of DCC (227mg, 1mmol) in $CHCl_3$ at -10°C in the same manner at VI_a. Yield 358mg(97.8%), oil, $[\alpha]_D^{23}$-92.5°(c-0.4, EtOAc). VI_b was detected by the positive aziridine test[6]. NMR($CDCl_3$): δ: 1.14ppm(3H d, 5.8Hz, $C\underline{H}_3$-CH-); 2.15ppm(1H o, 5.8, 6.8Hz, β-proton); 3.05ppm(1H d, 6.8Hz(cis), α-proton); 3.67ppm(2H s C_6H_5-$C\underline{H}_2$-); 5.09ppm(2H s C_6H_5-$C\underline{H}_2$-O-); 5.66, 6.17ppm(2H 2q 5.0, 18Hz, 6.5, 18Hz, -NH-$C\underline{H}_2$-). IR_{KBr} : 1705cm^{-1}(-CO-N=(aziridine)). Anal Found: C, 68.63; H, 6.07; N, 7.71%. Calcd for $C_{21}H_{22}O_4N_2$: C, 68.83; H, 6.05; N, 7.65%.

Z-D-PhGly-3-Me-L-Azy-Gly-OBzl (VI_c)

Z-D-PhGly-OH(1.82g, 6.4mmol) was coupled with V(1.88g, 7.6mmol) by the aid of DCC (1.57g, 7.6mmol) in $CHCl_3$ at -10°C in the same manner at VI_a. Yield 1.76g(64.9%), mp 129-133°C, $[\alpha]_D^{23}$-102.6°(c=1.0, $CHCl_3$). VI_c was detected by the positive aziridine test[6]. NMR($CDCl_3$):δ; 1.12ppm(3H d, 6.0Hz, $C\underline{H}_3$-CH-); 2.53ppm(1H m, β-proton); 3.28ppm(1H d, 6.7Hz(cis), α-proton); 5.01, 5.10ppm(4H 2s,C_6H_5-$C\underline{H}_2$-O, C_6H_5-$C\underline{H}_2$-CO); 5.30ppm(1H d, 6.5Hz, C_6H_5-C$\underline{H}$), 3.55, 4.13ppm(2H 2q, 5.0, 19Hz, 6.5, 19Hz, -NH-$C\underline{H}_2$-). Anal Found: C, 67.77; H, 5.72; N, 7.89%. Calcd for $C_{29}H_{29}O_6N_3$: C, 67.56; H, 5.67; N, 8.15%.

Reference and Footnote

1) Part IV: Y. Nakagawa, T. Tsuno, K. Nakajima, M. Iwai, H. Kawai, and K. Okawa, Bull. Chem. Soc. Japan, 45 1162 (1972). The abbreviations used throughout this work are essentially those recommended by the IUPAC-IUB Commission on Biochemical Nomenclature, as published in J. Biol. Chem., 247 977 (1972).
We have used "Azyline" as the name of an aziridine carboxylic acid and "Azy" as an abbreviation of azyline.
2) J. Smrt, J. Beranek, and J. Sicher, Chem. Abstr., 55, 10468i (1961); U.S. 2958691 Nov. 1, 1960.
3) K. Okawa, T. Kinutani, and K. Sakai, Bull. Chem. Soc. Japan, 41 1353 (1968).
4) D.F. Elliott, J. Chem. Soc., 1950, 62.
5) A.F. Wagner, J. Amer. Chem. Soc., 79, 3240 (1957).
6) R. Preussmann, H. Schneider, and F. Epple, Arz neimittel-Forsch., 19 1059 (1969).
7) L. Zervas, J. Amer. Chem. Soc., 81, 2884 (1959).

(Received April 9, 1975)