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THE STEREOSELECTIVE FORMATION OF THREONINE FROM cis- AND trans-1-α-METHYLBENZYL-2-METHOXYCARBONYL-3-METHYL AZIRIDINES

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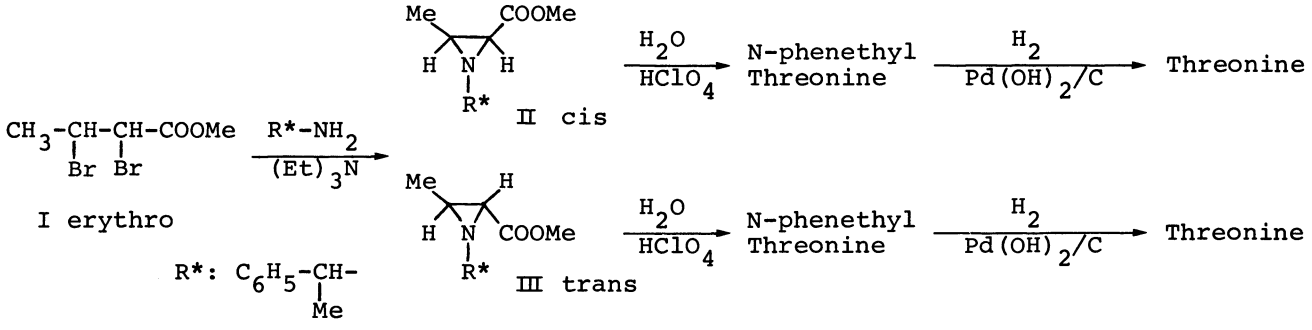
The reaction of methyl α,β-dibromobutyrate with α-methylbenzylamine resulted in the formation of cis- and trans-1-α-methylbenzyl-2-methoxycarbonyl-3-methyl aziridines(II and III), which were converted to threonine predominantly upon the hydrolytic ring opening of the aziridines.

It has been known that aziridine carboxylic acid could be converted to β-hydroxy-α-amino acid by the hydration reaction.[1,2] Generally, a high stereospecificity was observed[2-5] in this type of reaction. Recently, the synthesis and the NMR study on the cis- and trans-1-benzyl-2-methoxycarbonyl-3-methyl aziridines were reported.[6] However, the detailed study on the stereochemistry of the hydration reaction of the aziridine carboxylic acid have not been reported.

In this study, the reaction of methyl α,β-dibromobutyrate and α-methylbenzylamine was studied. To the solution of methyl α,β-dibromobutyrate(0.02 mole) in ethanol(50 ml) containing triethylamine(0.06 mole), DL-α-methylbenzylamine(0.02 mole) was added slowly, and the solution was kept at 50 °C for 24 hrs. From the reaction mixture, cis-1-α-methylbenzyl-2-methoxycarbonyl-3-methyl aziridine(II)(mp 87°, 20%)[7] and trans-1-α-methylbenzyl-2-methoxycarbonyl-3-methyl aziridine(III)(oil, 24%)[8] were obtained by silica gel column chromatography. The compounds II and III were each treated with 20% perchloric acid at 80 °C for 30 hrs. The resulting N-phenethyl-β-hydroxy-α-amino acid was separated by using a Dowex-50 column. This was applied for hydrogenolysis using palladium hydroxide on charcoal at room temperature for 24 hrs. The resulting amino acid was isolated by using Dowex-1 and Dowex-50 columns. The amino acid was examined by an amino acid analyzer, IR, NMR[9] and TLC.[10] The amino acid obtained from II was composed mainly of threonine(yield 87% from II, threo : erythro = 1 : 0.21). The amino acid obtained from III was also composed mainly of



threonine(yield 83% from III, threo : erythro = 1 : 0.10). The results indicate clearly that the normal stereospecific hydrolytic ring opening mechanism of aziridine can not be applied in the reactions of the compounds II and III. The reaction mechanism is not clarified yet, however, the result might suggest that both reactions pass through the same intermediate in the sterically controlled reactions.

In order to obtain further information on the hydrolytic ring opening of aziridine, asymmetric syntheses of compounds II and III were carried out using (S)-(-)-α-methylbenzylamine. Methyl α,β-dibromobutyrate was treated with (S)-(-)-α-methylbenzylamine in a similar way, and optically active II and III were obtained after column purification {II, 20.3%, $[\alpha]_D^{25}$: -96.2° (c 0.91, EtOH); III, 21.2%, $[\alpha]_D^{25}$ + 37.7° (c 1.37, EtOH)}. After the hydrolytic ring opening of optically active II and subsequent hydrogenolysis, optically active threonine {$[\alpha]_D^{25}$ = -12.1° (c 1.20, H_2O), threo : erythro = 1 : 0.18} was obtained in 82% from II. From optically active III, threonine {$[\alpha]_D^{25}$ = +19.7° (c 1.24, H_2O), threo : erythro = 1 : 0.08} was also obtained in 82% yield from III. Reported $[\alpha]_D^{25}$ for L-threonine is -28.3° (c 6.0, H_2O).[11] The resulting optically active threonine contains a small amount of allothreonine, therefore it is difficult to express the optical purity of the product. However, the $[\alpha]_D^{25}$ values of the threonine indicate the high stereoselectivity in the formation of optically active threonine.

References and Notes

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7) δ($CDCl_3$) 1.11 - 1.21(d, 3H, $C\underline{H}_3$-CH-N), 1.37 - 1.48(d, 3H, Ph-CH($C\underline{H}_3$)-N), 1.73 - 2.03(m, β-H, ring proton), 2.17 - 2.28(d, α-H, J = 6.6 Hz, ring proton), 2.44 - 2.78(q, 1H, Ph-C$\underline{H}$(CH_3)-N), 3.70(S, 3H, -$CO_2C\underline{H}_3$), 7.08 - 7.40(m, 5H, aromatic H).
8) δ($CDCl_3$) 1.23 - 1.39(3H, $C\underline{H}_3$-CH-N), 1.39 - 1.53(d, 3H, Ph-CH($C\underline{H}_3$)-N), 1.81 - 2.20(m, β-H, ring proton), 2.12(S, α-H, ring proton), 2.44 - 2.79(q, 1H, Ph-C$\underline{H}$(CH_3)-N), 3.62(S, 3H, -$CO_2C\underline{H}_3$), 7.03 - 7.46(m, 5H, aromatic H).
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