STERICALLY CONTROLLED SYNTHESIS OF cis-1-BENZYL-2-METHOXYCARBONYL-3-PHENYLAZIRIDINE

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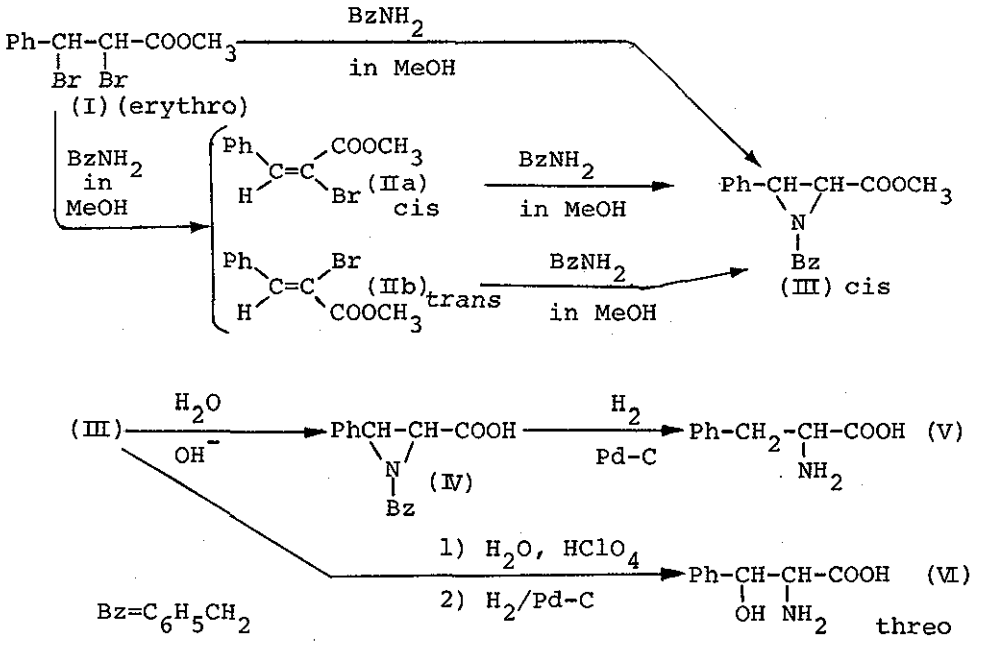
The treatment of methyl erythro-2,3-dibromo-3-phenylpropionate(I), methyl cis- and trans-α-bromocinnamate(IIa, IIb) with benzylamine resulted in the formation of the same sole product cis-1-benzyl-2-methoxycarbonyl-3-phenylaziridine(III). A plausible stereochemical pathway was discussed. The compound III was converted to phenylalanine(V) by hydrogenation and threo-β-phenylserine(VI) by hydration reaction.

Several studies on the synthesis of aziridine from α,β-dihalogen compounds[1-6], and also some stereochemical studies on the formation of trans-aziridine have been reported[7-10]. Recently, a sterically controlled synthesis of cis-aziridine from erythro-1-menthyl 2,3-dibromo-3-phenylpropionate was reported[11]. It was explained that the dibromide was converted to a more stable 1-menthyl 2-bromocinnamate(trans form) which upon treatment with ammonia gave cis-aziridine. If this is the case, cis-2-bromocinnamate would result in the formation of trans-aziridine.

In this communication, sterically controlled synthesis of

cis-1-benzyl-2-methoxycarbonyl-3-phenylaziridine(III) from methyl erythro-2,3-dibromo-3-phenylpropionate(I), methyl cis- and trans-α-bromocinnamate(IIa , IIb) is described. The resulting III was converted to phenylalanine(V) by hydrogenolysis and to threo-phenylserine(VI) by hydration and subsequent hydrogenolysis (Scheme 1).



Scheme 1

To a solution of compound I(erythro)(18.0 g, 0.054 mole) in methanol(100 ml), benzylamine(23.1 g, 0.216 mole) was added slowly and the mixture was stirred for 24 hr at 35 - 40 °C. After the reaction was over, methanol was evaporated under reduced pressure and the residual material was extracted with

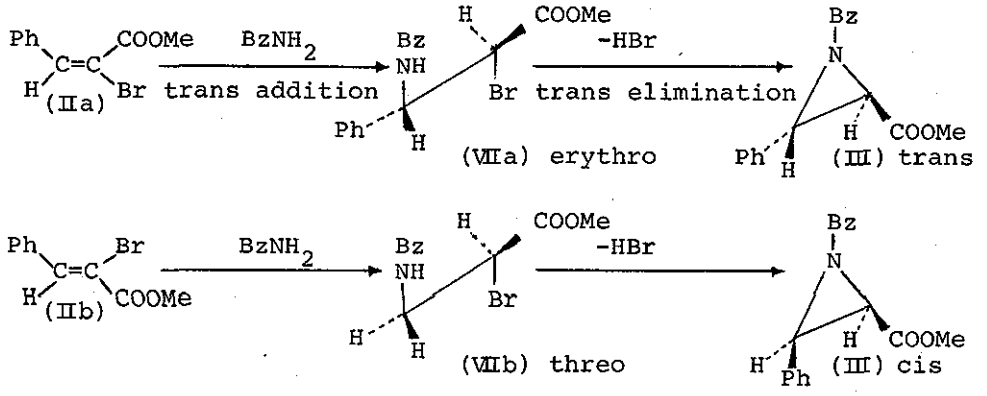
ethyl acetate, and the extract was washed with 3% hydrochloric acid and water. The ethyl acetate solution was dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residual crude III was recrystallized from methanol and water to afford compound(III)(11.5 g; 80%), mp 64 - 65 °C. The structure of cis-aziridine(III) was determined by elemental, IR and NMR analyses[12].

The compound I(2.0 g, 0.006 mole) was treated with an equivalent mole of triethylamine or benzylamine in methanol (30 ml) at room temperature for 24 hr. The solvent was evaporated and the reaction product was extracted with ethyl acetate, thus α-bromocinnamate being obtained in 93% yield. The NMR analysis shows that the compound is composed of about an equal amount of methyl cis- and trans-α-bromocinnamate(IIa and IIb)[13]. The compounds IIa and IIb were separated by alumina column chromatography(diameter 1.6 cm, length 25 cm) using benzene:n-hexane(1 : 5) as the elution solvent. The methyl cis-α-bromocinnamate(IIa) was eluted first and methyl trans-α-bromocinnamate(IIb) was eluted second. These were oily material and did not crystallize. The structure of IIa and IIb was confirmed by IR and NMR analyses[13]. The cis-compound IIa (1.00 g, 0.004 mole) in methanol(30 ml) was mixed slowly with 1.28 g(0.012 mole) of benzylamine and the mixture was treated in the same way as described in the reaction of the compound I with benzylamine. The physical properties of resulting aziridine(1.9 g, 89%, mp 64 - 65 °C) were identical with those

of aziridine(III) obtained directly from compound I. The NMR analysis indicates that the structure of the aziridine obtained from IIa is cis-form[12]. In the same way, the trans-compound IIb was treated with benzylamine and cis-aziridine(III)(83%, mp 64 - 65 °C) was also obtained[12].

The compound III could not be hydrogenolyzed to methyl phenylalaninate by the use of palladium on charcoal or palladium hydroxide on charcoal at atmospheric pressure of hydrogen. The compound III(2.7 g, 0.01 mole) was saponified with two equivalent amount of methanolic aqueous sodium hydroxide(MeOH : H_2O = 4 : 1) and aziridine carboxylic acid(IV) (yield, 2.2 g, 87%, mp 107 °C) was obtained[14]. The compound IV was hydrogenolyzed to form phenylalanine(V)(88%) by palladium hydroxide on charcoal at room temperature under atmospheric pressure of hydrogen in methanolic aqueous solution(MeOH : H_2O = 6 : 4). The compound III(0.50 g, 0.002 mole) was also treated with 20% aqueous perchloric acid(30 ml) at 80 °C for 30 hr[15]. After the hydration reaction was over, perchloric acid was precipitated as potassium perchlorate and the resulting N-benzylphenylserine was isolated by a Dowex 50 column, and then hydrogenolyzed to phenylserine(VI) by the use of 5% palladium on charcoal. The composition of the crude phenylserine was determined by the use of an amino acid analyzer(Yanagimoto Model LC-5S) and paper and thin layer chromatography using a solvent which separates threo- and erythro-phenylserine[16]. The yields of amino acids from III are: threo-phenylserine(64%), erythro-phenylserine(5.3%) and

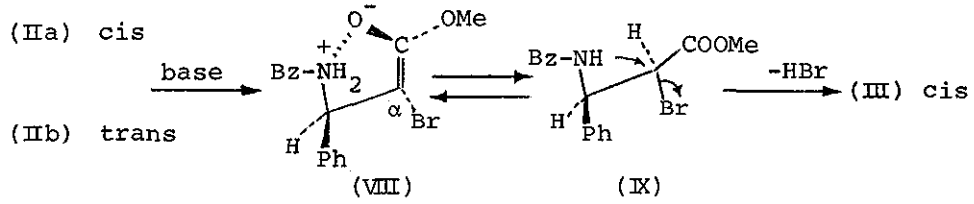
glycine(3.3%). The presence of phenylisoserine(threo and erythro) was not identified in the reaction mixture. Therefore the hydration reaction seems to proceed mostly or entirely in a way to form α-amino acids. The formation of threo-phenylserine by the hydration reaction(trans addition) of III also supports the cis-structure of III. Both amino acids (V) and (VI) are confirmed by elemental, IR, NMR and amino acid analyses in comparison with the authentic samples.



Scheme 2

The compounds IIa and IIb were expected to form methyl erythro- and threo-α-bromo-β-benzylamino-β-phenylpropionate(VIIa and VIIb) by trans addition of benzylamine(Scheme 2). The compounds VIIa and VIIb would form stereospecifically trans- and cis-aziridine(III trans, III cis) by trans-elimination of hydrogen bromide in the presence of a base. However, the fact that cis- and trans-bromocinnamate(IIa and IIb) resulted in the formation of the same sole product, cis-aziridine(III), indicates that the

above mentioned normal addition and elimination mechanism is not applicable to the formation of III from both IIa and IIb. Therefore, it could be assumed that IIa and IIb passed through the same intermediate in the cis-aziridine(III) formation, probably during the reaction from VII to III. A possible stereochemical explanation for the formation of the cis-aziridine is shown in Scheme 3 [10]. The carbonyl group of VIIa and VIIb is



Scheme 3

enolized in the presence of a base to form an intermediate compound(VIII). The α-carbon of VIII, which has the sp^2 structure, is then protonated at the less bulky side of the molecule to form compound IX, and the subsequent cyclization reaction to form aziridine III takes place by trans-elimination of hydrogen bromide. If this is the case, the formation of cis-aziridine from compounds I, IIa and IIb could be explained reasonably.

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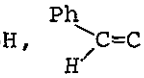
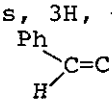
12 III : δ($CDCl_3$) 2.51-2.69(dd, 2H, J = 6.6 Hz, aziridine ring H), 3.58(s, 3H, $-COOCH_3$), 3.08(ABq, 2H, J = 6.0 Hz, N-methylene), 7.01-7.47(m, 10H aromatic H); T. J. Batterham, "NMR Spectra of Simple Heterocyles", pp 137 - 140, John Wiley & Sons, New York (1973), trans:J = 2-2.7 Hz,

cis:J = 5-6 Hz.

13 IIa : δ($CDCl_3$) 3.64(s, 3H, $-COOCH_3$), 7.16-7.27(m, 6H, 
cis and aromatic 5H). IIb : δ($CDCl_3$) 3.76(s, 3H, $-COOCH_3$),
7.85-7.18(m, 5H, aromatic 5H), 8.07(s, 1H,  ; IIa and IIb were saponified with alkali and obtained cis- and trans-α-bromocinnamate(mp 120° and 131 °C respectively). The IR and NMR data agreed with those of the authentic cis- and trans-α-bromocinnamate prepared separately.

14 IV : δ($CDCl_3$) 2.63-3.39(dd, 2H, J = 6.6 Hz, aziridine ring H), 3.75(ABq, 2H, N-methylene), 7.00-7.47(m, 10H, aromatic H).

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