

Title	Synthetic studies on thiothreonine (I) synthesis of DL- α -amino- β -chlorobutyric acid and its derivatives
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Synthetic Studies on Thiothreonine (I)

Synthesis of DL- α -Amino- β -chlorobutyric Acid and its Derivatives

(Received August 10, 1951)

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Abstract

In connection with studies concerning the steric relation of thiothreonine-isomers with threonine-isomers which have been already established in steric constitutions, we prepared isomers of DL- α -amino- β -chlorobutyric acid and its derivatives. We chlorinated DL-allothreonine methyl ester hydrochloride with phosphorus pentachloride in absolute methanol and obtained DL- α -amino- β -chlorobutyric acid hydrochloride m. p. 189° C. (dec.) (IV) after hydrolysis. This chloroderivatives gives DL- α -benzamido- β -chlorobutyric acid m. p. 173-174° C. (V) and ethyl DL- α -benzamido- β -chlorobutyrate m. p. 99-100° C. (dec.) (VI). Starting with DL-threonine we obtained corresponding diastereoisomers IV', V' and VI' which melted at 196-197° C. (dec.), 142-143° C. and 84.5-86.5° C. respectively. Thiol derivatives will be described in the next report.

Introduction

Thiothreonine was synthesized by H. E. Carter et al.¹⁾ in 1941 by means of the additive reaction of benzylmercaptane to benzoyl- α -amino crotonic acid azlactone. Although many synthetic studies about cysteine and penicillamine, both of which are homologues of thiothreonine, have been reported, there has been no attempt done about the thiothreonine except the latest report of D. F. Elliot²⁾, in which he attempted to synthesize the thio amino acids through related thiazolines. Regarding the threonine, steric relations among its four diastereoisomers have been

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1) H. E. Carter, C. M. Stevens and L. F. Ney, J. Biol. Chem., **139**, 247 (1941)

2) D. F. Elliot, Nature, **162**, 658-9 (1948); C. A., **43**, 3786 (1949)

3) McCoy, Meyer and Rose, J. Biol. Chem., **115**, 721 (1935); H. D. West, H. E. Carter, J. Biol. Chem., **119**, 109-119 (1937); J. Biol. Chem., **122**, 611 (1937-38); D. F. Elliot, J. Chem. Soc., 62 (1950)

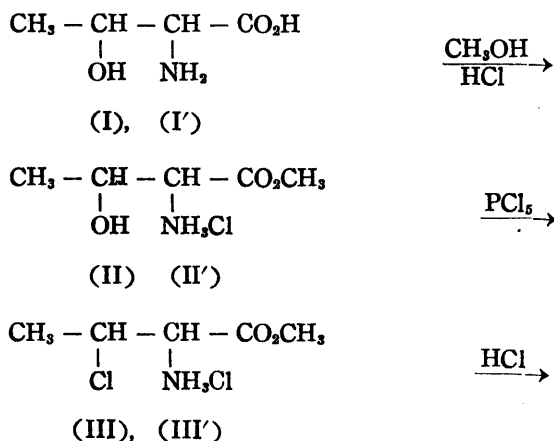
solved recently³⁾, while relations between these diastereoisomers of threonine and those of thiothreonine have not been made clear at all.

We have made several investigations in order to obtain some valuable proofs which show steric relations between threonine and thiothreonine. In this paper, we synthesized two kinds of racemic isomers of DL- α -amino- β -chlorobutyric acid and their derivatives and obtained some new compounds.

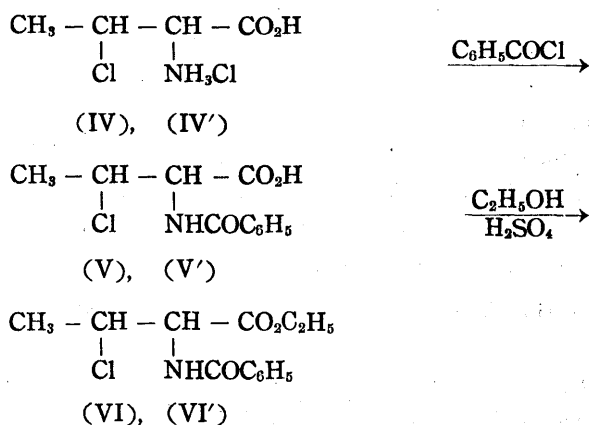
Starting from DL-threonine and DL-allothreonine, both of which are racemic diastereoisomers and are known about their steric configurations clearly, we intended the replacement of hydroxyl groups on β -carbon atoms of these two diastereoisomers by chlorine atoms and then the replacement of the chlorine atoms by sulfhydryl groups. Although cysteine⁴⁾ is synthesized by a analogous route, we made this investigation with interest in the important problem about the relation between the steric configuration and the replacement-reaction on the asymmetric β -carbon atom of thiothreonine. In the case of cysteine it is out of question.

We esterified DL-allothreonine (I) with absolute methanol and hydrogen chloride gas, and obtained DL-allothreonine methylester hydrochloride (II), m. p. 150° C (dec.). II was chlorinated to methyl DL- α -amino- β -chlorobutyrate hydrochloride (III), m. p. 161° C (dec.), with phosphorus pentachloride in acetyl chloride and the saponification of III gave DL- α -amino- β -chlorobutyric acid hydrochloride (IV), m. p. 189° C (dec.) easily. The benzoyl derivative of IV, m. p. 174-174° C, prepared by Schotten-Baumann's method was also esterified with absolute ethanol and sulfuric acid, giving ethyl DL- α -benzamido- β -chlorobutyrate (VI) m. p. 99-100° C.

Starting from DL-threonine (I'), we could obtain corresponding diastereoisomers, II' m. p. 125° C (dec.), III' m. p. 173° C (dec.), IV', m. p. 196-197° C (dec.), V' m. p. 142-143° C and VI' m. p. 84.5-86.5° C by analogous processes.



4) E. Fischer, K. Raske, Ber., 41, 893 (1908); J. L. Wood, L. van Middlesworth, J. Biol. Chem., 179, 529 (1949)



Now, if we assume that the chlorine-replacement with phosphorus pentachloride was presumably accompanied by Walden inversion, it can be considered that each of DL- α -amino- β -chlorobutyric acids, IV and IV' has the steric structure corresponding to DL-threonine and DL-allothreonine respectively. Both racemic isomers of DL- α -amino- β -chlorobutyric acid were obtained with good yields.

Experimental

i) (A) *DL-Allothreonine methylester hydrochloride* (II) : a suspension of 1.5 g of DL-allothreonine (m. p. 242°C) (I) in 45 cc of absolute methanol was saturated with dry hydrochloric acid gas without cooling. After leaving it away from moisture overnight, methanol was distilled off under reduced pressure (below 45°C). The syrupy residue crystallized on standing over P_2O_5 under reduced pressure. In order to complete the esterification, the crude material was dissolved in absolute methanol and the same operation as described above was repeated. The crude methyl ester hydrochloride of DL-allothreonine (II) was dissolved in a small amount of dry methanol, and added with absolute ether slowly. We obtained colorless needles which were very hygroscopic. The melting point of this sample was not distinct. It began to sinter with a little foaming at 139-140°C, and decomposed at about 150°C under evolving of gas. 2.1 g., (98%) (Found: N, 8.18; Calculated for $\text{C}_5\text{H}_{12}\text{O}_3\text{NCl}$: N, 8.26)

(B) *DL-Threonine methyl ester hydrochloride* (II') : 1 g. of DL-threonine (m. p. 127-8°C) was treated by the same method as described above (A), yielding very hygroscopic colorless needles (II'). 1.33 g. (94%). This began to sinter with a little foaming at 117-8°C and decomposed under evolving of gas at about 125°C (Found : N, 8.02, Calculated for $\text{C}_5\text{H}_{12}\text{O}_3\text{NCl}$: N, 8.26)

ii) *Methyl DL- α -amino- β -chlorobutyrate hydrochloride* (III, III') (A) The preparation of III from DL-allothreonine methyl ester hydrochloride (II) : In a glass-stoppered Erlenmeyer's flask which was cooled in an ice bath 1.5 g. of II

was suspended in 6 cc. of fresh distilled acetyl chloride and added with 2.3 g. of roughly pulverized fresh phosphorus pentachloride under shaking. Immediately the content of the flask became a crystalline mass. After shaking for half an hour, crystals were filtered off, washed with acetyl chloride and finally with dried petroleum ether. m. p. 156-160°C, 1.25 g. (75%). This crude material was dissolved in absolute methanol which contained hydrochloric acid gas slightly and added with ether, yielding colorless fine needles (III), m. p. 160-161°C (dec.) (Found N, 7.22, Calculated for $C_8H_{11}O_2NCl$: N, 7.45)

(B) The preparation of III' from DL-threonine methylester hydrochloride (II') : 1.2 g of II' were chlorinated by the same method as described above (ii) (A). The yield was 0.9 g (68%). This was recrystallized from absolute methanol containing hydrochloric acid gas slightly and dried ether, yielding colorless fine long needles (III), m. p. 173°C (dec.) (Found. N, 7.14 ; Calculated for $C_8H_{11}O_2NCl$: N. 7.45)

iii) *DL- α -Amino- β -chlorobutyric acid hydrochloride (IV IV')* (A) The preparation of IV from methyl DL- α -amino- β -chlorobutyrate hydrochloride (III) : 2g of III was refluxed with 20 cc of 20 % hydrochloric acid for 1.5 hours on a water bath. The reaction product was evaporated to dryness in vacuo. The crystalline mass, 1.7 g (98%), was recrystallized from absolute methanol and absolute ether, giving colorless plate-form crystals (IV), melting at 189°C (dec.). (Found : C, 27.67 ; H, 5.47, Calculated for $C_4H_9O_2NCl_2$: C, 27.59 ; H, 5.24)

(B) The preparation of IV' from methyl DL- α -amino- β -chlorobutyrate hydrochloride (III) : 1.1 g of III was saponified by the same procedure as described in (iii) (A), yielding 1.5 g of crude material (95%). Recrystallization from absolute methanol and dried ether gave colorless fine crystals (IV) melting at 196-197°C (dec.) (Found : N, 7.95 ; Calculated for $C_4H_9O_2NCl_2$: N. 8.05)

iv) *DL- α -Benzamido- β -chlorobutyric acid (V, V')* (A) The preparation of V from DL- α -mino- β -chlorobutyric acid hydrochloride (IV) : A solution of 1 g. of IV in 7.2 cc of 4N sodium hydroxide was treated with 1.18 g. of benzoylchloride under ice cooling. When the reaction was complete, the solution was acidified with conc. hydrochloric acid under cooling in ice bath. The precipitate was separated by filtration, dried, and extracted with 6 cc of hot carbon tetrachloride on water bath twice to remove benzoic acid. The crude benzoyl derivative (V) melted at 172-173°C. The yield was 0.83 g (60%). Recrystallization from water gave colorless plateform crystals (V), melting at 173-174°C. (Found : N, 5.57 ; Calculated for $C_{11}H_{13}O_2NCl$; N, 5.80).

(B) The preparation of V from DL- α -amino- β -chlorobutyric acid hydrochloride (IV) : 1g of IV was benzoylated as described above (iv) (A). But, in this case, the first precipitated crude benzoyl derivative was combined with the second one

obtained by the vacuum-concentration of the acidic filtrate. The combined dried product was treated with carbon tetrachloride described above (iv) (A) and gave almost pure material (V'). The yield was 0.88 g (65%). Recrystallization from water gave colorless platform crystals, melting at 142-143°C which is more soluble than V. (Found : N, 5.96, Calculated for $C_{11}H_{12}O_3NCl$ N, 5.80)

v) Ethyl DL- α -benzamido- β -chlorobutyrate (VI, VI'). (A) The preparation of VI from DL- α -benzamido- β -chlorobutyric acid (V) : A suspension of 1 g of V in 20 cc of absolute ethanol and 0.17 cc of conc. sulfuric acid was refluxed for two hours on a water bath. 0.2 cc of distilled water was added, and then solid sodium bicarbonate added until the mixture became neutral to congo red. The filtered solution was concentrated to a syrup under reduced pressure and the residue was taken up in benzene. The benzene extract was concentrated again to a crystalline mass. The light-yellow crude ethyl ester of V, 0.6 g, (54%) was recrystallized from petroleum ether. Colorless prisms melting at 99-100°C. (Found N, 4.67 ; Calculated for $C_{13}H_{16}O_3NCl$: N, 5.20)

(B) The preparation of VI from DL- α -benzamido- β -chlorobutyric acid (V') : The esterification of 0.5 g. of V yielded 0.2 g. (52%) of crude ester (VI) by the same operation as described in (iv) (A). By recrystallization from petroleum ether colorless needles were obtained. This sample melted at 84.5-86.5°C. (Found : N, 4.67 ; Calculated for $C_{13}H_{16}O_3NCl$: N, 5.20) Elliot⁵⁾ has succeeded in producing these compounds (VI and VI') by a different method recently.

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5) D. F. Elliot, J. Chem. Soc., 589-94 (1949) ; C. A., 43, 9033 (1949)