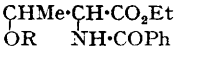
126. *The Stereochemistry of an Oxazoline Derivative of Threonine. Improvement of a Recent Threonine Synthesis.*

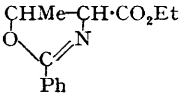
By D. F. Elliott.

The preparation of some 2-phenyl-substituted oxazoline esters by reaction of benziminoethyl ether with ester hydrochlorides of serine and threonine is described.

In the threonine series this occurs with retention of configuration at both asymmetric centres. The *cis*-configuration of the oxazoline derived from *allo*threonine was unstable in the presence of aqueous alkali and was transformed into the *trans*-configuration with simultaneous hydrolysis of the ester group. This discovery was utilised for the improvement of a recent threonine synthesis.

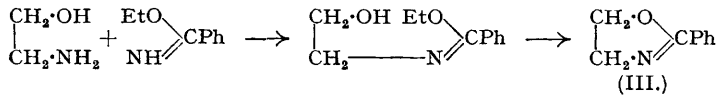
In a previous paper (Attenburrow, Elliott, and Penny, *J.*, 1948, 310) it was shown that *N*-benzoyl*allo*threonine ethyl ester (as I) or its *O*-tosyl derivative could be converted into the corresponding oxazoline (II) with inversion of configuration at the β-carbon atom by the action of thionyl chloride or potassium acetate.

(I.) 


(II.)

As part of a programme of research concerned mainly with the isolation of threonine from proteins, a search has been made for a method of preparing the oxazoline (II) in which configur-

ation would be retained at both carbon atoms in the threonine molecule. Barber, Gregory, Slack, Stickings, and Woolman (C.P.S. 66, May 24th, 1944) showed that 2-phenyl-Δ^2-oxazoline (III) was obtained when ethanolamine was heated with benziminoethyl ether. They considered that an open-chain, substituted iminoether was first formed and then cyclised at the higher temperature with elimination of alcohol.

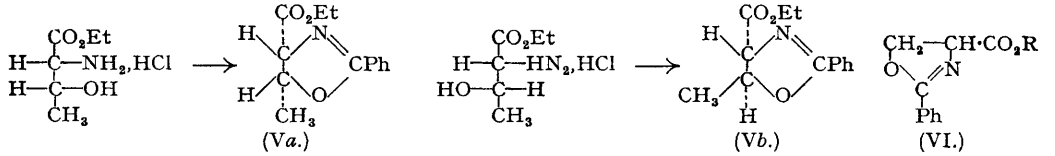


(III.) $R{\cdot}C(OR_1){:}N{\cdot}CH_2{\cdot}CO_2Et$ (IV.)

N-Substituted iminoethers (IV) derived from glycine ethyl ester were described by Schmidt (*Ber.*, 1914, **47**, 2548) and recently by Cornforth and Cornforth (*J.*, 1947, 96). The latter authors studied the reaction in great detail with a variety of iminoethers. A concentrated aqueous solution of glycine ester hydrochloride was shaken with the iminoether in the presence or absence of a solvent such as ether at room temperature. After a certain time the product was isolated by distillation. It will be noted that the hydrochloride of the base was used and not the free base as in the experiments of Barber *et al.* (*loc. cit.*). It seemed probable that a compound analogous to (IV) could be prepared from threonine, but the conditions required for the cyclisation remained to be determined. It was thought that this would be brought about by the action of heat if the suggestions of Barber *et al.* (*loc. cit.*) were correct. The question of the configuration of the product could not be decided with certainty, but it seemed probable that it would be the same as that of the starting material.

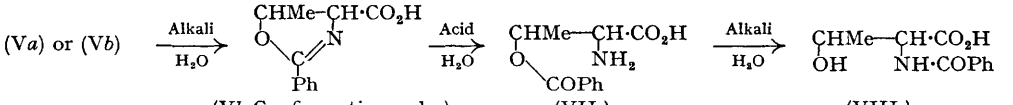
When allo*threonine ethyl ester hydrochloride* reacted with benziminoethyl ether under the conditions of Cornforth and Cornforth (*loc. cit.*), it was surprising to find that cyclisation had occurred in the cold to give a good yield of cis-4-*carbethoxy*-2-*phenyl*-5-*methyl*-Δ^2-*oxazoline* (V*a*). Hydrolysis of this oxazoline with hydrobromic acid yielded pure *allo*threonine, thus confirming the configuration assigned to it. In a similar way *threonine ethyl ester hydrochloride* gave *trans*-4-carbethoxy-2-phenyl-5-methyl-Δ^2-oxazoline (V*b*). The configuration of this oxazoline was also known; it was identical with the one described by Attenburrow *et al.* (*loc. cit.*), which yielded threonine on acid hydrolysis. The two oxazolines (V*a*) and (V*b*) differed substantially in refractive index and in the melting points of the picrates, and a mixture of the two picrates had a melting point below that of either pure substance. It was concluded that no appreciable inversion had occurred in either case.

In the course of this work it was noted that *allo*threonine ethyl ester hydrochloride was easily soluble in hot acetone, whereas the threonine analogue was almost insoluble unless some alcohol was present. It is possible that a mixture of the two amino-acids could be separated into its constituents by making use of this fact.



(V*a*.) (V*b*.) (VI.)

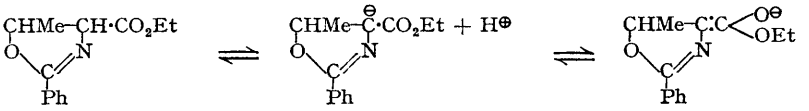
The above-described reactions with benziminoethyl ether were also extended to ester hydrochlorides of serine. It was found that the yield of oxazoline became progressively greater as the size of the alkyl group in the ester was increased. 4-Carbomethoxy-2-phenyl-Δ^2-oxazoline (VI, R = Me), 4-*carbethoxy*-2-*phenyl*-Δ^2-*oxazoline* (VI, R = Et), and 4-*carbo*iso*propoxy*-2-*phenyl*-Δ^2-*oxazoline* (VI; R = Pr^i) were obtained in 40, 59, and 81% yields respectively under the same conditions. The methyl ester (VI; R = Me) was prepared by Bergmann and Miekeley (*Z. physiol. Chem.*, 1924, **140**, 128) by cyclisation of benzoylserine methyl ester with thionyl chloride and was described as a liquid. It was obtained by the present method as a low-melting solid. The following series of transformations was next studied :



(V*a*) or (V*b*) (V*b* Configuration only.) (VII.) (VIII.)

A similar sequence in the serine field starting from the oxazoline ester (VI; R = Me) was first described by Bergmann and Miekeley (*loc. cit.*). In the present investigation it was found that

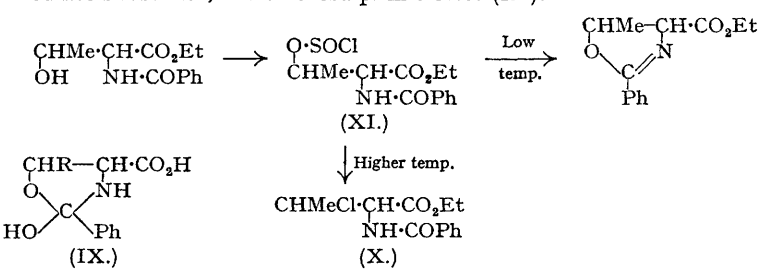
the oxazolines (V*a* and V*b*) both gave the same *2-phenyl-5-methyl-Δ²-oxazolinecarboxylic acid* on treatment with dilute aqueous alkali at the boiling point. When dissolved in cold dilute hydrochloric acid and kept at room temperature for several hours the oxazolinecarboxylic acid was converted into the hydrochloride of *O-benzoylthreonine* (VII), the free base being obtained when the solution was cautiously neutralised to pH 4—5 with ammonia or sodium acetate. Treatment of the *O*-benzoyl compound with dilute aqueous alkali led to the formation of *N*-benzoylthreonine. These experiments show that the oxazolinecarboxylic acid most probably had the *trans*-structure (V*b*) derived from threonine. The most likely way in which the *cis*- was transformed into the *trans*-oxazoline was by intermediate formation of the ester anion :



In the absence of alkali the *cis*-oxazoline ester was quite stable, because it was not changed by distillation at a moderately high temperature and showed no change in refractive index on standing for 14 days. If the scheme given above is correct, the conversion of the *cis*- into the *trans*-form was the result of a true equilibrium, and it is fortunate that steric factors favoured the *trans*-form to the almost complete exclusion of the *cis*-form. As far as could be ascertained, the final product (VIII) was obtained pure from both oxazoline esters, but a small amount of *N*-benzoyl*allo*threonine (arising from V*a*) would not have been detected. It was safe to assume that the final product contained at least 90% of *N*-benzoylthreonine.

The compound (VII) behaved like a normal organic acid and not like an amino-acid on titration in aqueous solution. The end-point to phenolphthalein was quite sharp, and immediate acidification liberated *N*-benzoylthreonine. *O*-Acylated 1 : 2-hydroxyamino-compounds in general are known to display this rapid migration of the acyl group under the influence of alkali, and Bergmann, Brand, and Weinmann (*Z. physiol. Chem.*, 1923, **121**, 1) have suggested that a cyclic intermediate (IX) may be involved. The existence of such a compound has never been proved (in this connection, see Phillips and Baltzly, *J. Amer. Chem. Soc.*, 1947, **69**, 200).

In the synthesis of threonine from hippuric acid described by Attenburrow, Elliott, and Penny (*loc. cit.*) ethyl α-benzamido-β-hydroxybutyrate was obtained as an intermediate product. It was necessary to separate this compound into the two stereoisomeric forms before completion of the synthesis, and as a result considerable losses occurred. This separation has now been rendered unnecessary, because of the favourable steric influences operating in the oxazolines (V). The conditions employed by Attenburrow *et al.* (*loc. cit.*) for the cyclisation of the ester (I; R = H) with thionyl chloride were not entirely satisfactory when large amounts of crude ethyl α-benzamido-β-hydroxybutyrate were being handled. This reaction was therefore submitted to further study. Sudden rises of temperature were frequently encountered when the reaction mixture was removed from the cooling bath, although the reaction had apparently ceased. In these cases the product was always contaminated with a considerable amount of *ethyl β-chloro-α-benzamidobutyrate* (X). The structure of this substance was confirmed by its hydrolysis by alkali to α-benzamidocrotonic acid and conversion of the latter into its azlactone (Carter, Handler, and Melville, *J. Biol. Chem.*, 1939, **129**, 359). The possibility that the chloro-compound was an intermediate in the formation of the oxazoline was eliminated when it was found that it did not give a trace of basic material on standing overnight with cold thionyl chloride. It seems most likely that the chloro-compound and the oxazoline were formed from the same intermediate substance, the chlorosulphinic ester (XI).



By carrying out the cyclisation slowly at low temperature, a very good yield of the oxazoline was obtained, and the formation of the chloro-compound was entirely suppressed. The mixture

of oxazoline esters (V*a* and V*b*) so obtained was then converted into *N*-benzoylthreonine by the series of changes already described. Isolation of the intermediate products was unnecessary; *N*-benzoylthreonine was obtained in about 60% overall yield from crude ethyl α-benzamido-β-hydroxybutyrate.

Experimental.

(M. p.s are uncorrected.)

Ester Hydrochlorides.—Except in one case, the ester hydrochlorides were prepared by suspending the amino-acid in 10—20 parts of the dry alcohol and passing in a rapid stream of dry hydrogen chloride until the solution boiled. It was then cooled, saturated with hydrogen chloride, kept overnight, then evaporated in a vacuum to a syrup and finally to complete dryness in an open dish in a vacuum desiccator over sodium hydroxide and sulphuric acid. The solid mass was then broken up, washed with dry ether, and crystallised from an anhydrous solvent. The products were generally hygroscopic solids. The yields recorded are for crude products. In most cases further purification was unnecessary. allo*Threonine ethyl ester hydrochloride* formed colourless rectangular plates from acetone, m. p. 117—118° (Found: N, 7·7. $C_6H_{14}O_3NCl$ requires N, 7·6%); yield 90%. *Threonine ethyl ester hydrochloride* crystallised in dense masses of prisms from a mixture of acetone (10 parts) and alcohol (3 parts) and had m. p. 118—119°, mixed m. p. with the above ester hydrochloride, 90°. It was dried at 60°/0·1 mm. for analysis (Found: N, 7·3; Cl, 19·65. $C_6H_{14}O_3NCl$ requires N, 7·6; Cl, 19·3%); yield 98·5%. Serine methyl ester hydrochloride had m. p. 134° as recorded by Painter (*J. Amer. Chem. Soc.*, 1947, **69**, 230) and not 114° as recorded by Fischer and Suzuki (*Ber.*, 1905, **38**, 4173); yield 77%. *Serine ethyl ester hydrochloride* formed colourless needles from ethanol–ether, m. p. 100—102°; it was very hygroscopic (Found: Cl, 20·5. $C_5H_{12}O_3NCl$ requires Cl, 20·9%); yield 95%.

Serine iso*propyl ester hydrochloride.* Serine (10 g.) was suspended in *iso*propyl alcohol (0·5% H_2O; 100 ml.), and a rapid stream of dry hydrogen chloride passed in until the solution boiled. The gas stream was then moderated and boiling continued by application of a small flame at such a rate that about 15 ml. of *iso*propyl alcohol escaped during 1 hour through the top of a 15″ air condenser fitted to the flask. After 30 minutes fresh *iso*propyl alcohol (15 ml.) was added to the contents of the flask. After 1 hour the alcohol was removed under reduced pressure, and the solid residue crystallised from *iso*propyl alcohol–ether; yield (of crystallised product) 14·3 g. (82%). It formed colourless prisms, m. p. 142—143° (Found: N, 7·4. $C_6H_{14}O_3NCl$ requires N, 7·6%). This *ester hydrochloride* was not hygroscopic.

Preparation of Oxazoline Esters from Serine and Threonine Esters.—After some exploratory experiments the following procedure was adopted for the preparation of the oxazolines. The ester hydrochloride (0·04 mol.) was dissolved in water (4 ml.) in a 250-ml. conical flask, mixed with a solution of benziminoethyl ether (9 g.) in ether (25 ml.), and the two layers vigorously shaken together for 8 hours (Griffin and Tatlock's " Microid " flask shaker was very suitable for the purpose). After addition of sufficient water to dissolve the ammonium chloride which had crystallised out, the upper layer was separated, washed three times with water, dried, and evaporated. In some cases a small amount of amorphous solid separated during the reaction. This did not dissolve on addition of water and it was necessary to filter the reaction mixture to obtain a clean separation of the two layers. The residue remaining was then distilled under reduced pressure, first at about 15—25 mm. to remove excess of the iminoether and then at 0·1 mm. or less.

4-Carbomethoxy-2-phenyl-Δ^2-oxazoline had b. p. 110—112/2 × 10^{-2} mm. and was a colourless oil which rapidly turned pale yellow in the receiver; yield 3·4 g. (41·5%). After several days the liquid solidified and was crystallised from ether–light petroleum (b. p. 40—60°). It formed sheaves of long prisms, m. p. 32—33° (Found: C, 64·4; H, 5·5; N, 6·9. Calc. for $C_{11}H_{11}O_3N$: C, 64·35; H, 5·4; N, 6·8%). The hydrochloride had m. p. 111—112° (Bergmann and Miekeley, *loc. cit.*, recorded m. p. 113—114°). The *picrate* was prepared by adding a solution of the oxazoline in dry ether to a solution of 1 equiv. of picric acid in dry ether. The crystalline precipitate was collected and crystallised from ethanol. It formed yellow prisms, m. p. 139—140° (Found: N, 13·25. $C_{17}H_{14}O_{10}N_4$ requires N, 12·9%).

4-*Carbethoxy-2-phenyl-*Δ^2-*oxazoline* had b. p. 106°/10^{-2} mm., $n_D^{18°}$ 1·5413, and was a fairly viscous liquid; yield 5·15 g. (59%) (Found: C, 65·4; H, 6·0; N, 6·5. $C_{12}H_{13}O_3N$ requires C, 65·7; H, 6·0; N, 6·4%). The *picrate*, prepared in the usual way, crystallised from alcohol as yellow prisms with pointed ends, m. p. 132° (Found: N, 12·7. $C_{18}H_{16}O_{10}N_4$ requires N, 12·5%).

4-*Carbo*iso*propoxy-2-phenyl-*Δ^2-*oxazoline* had b. p. 110°/10^{-2} mm. and rapidly solidified in the receiver; yield, 7·55 g. (81%). It was crystallised from light petroleum (b. p. 40—60°) and formed long colourless needles, m. p. 41—41·5° (Found: C, 67·1; H, 6·5; N, 5·75. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·5; N, 6·0%). The *picrate* formed yellow prisms from *iso*propyl alcohol; m. p. 134—135° (Found: N, 12·4. $C_{19}H_{18}O_{10}N_4$ requires N, 12·1%).

cis-4-*Carbethoxy-2-phenyl-5-methyl-*Δ^2-*oxazoline* had b. p. 124°/10^{-2} mm., $n_D^{19°}$ 1·5315; yield (after 6 hours' shaking) 6 g. (64·5%) (Found: C, 66·6; H, 6·6; N, 5·9. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·5; N, 6·0%). The *picrate* crystallised from ethyl alcohol in thin yellow plates, m. p. 148—150° (Found: N, 12·4. $C_{19}H_{18}O_{10}N_4$ requires N, 12·1%). In order to determine the nature of the product before distillation, a separate experiment was performed on a smaller scale and, after being dried, the ethereal extract was treated with ethereal picric acid in the cold. The crude picrate had a lower m. p. (132—138°), as would be expected, but the mixed m. p. with the pure picrate from the distilled oxazoline was 132—142°. This was taken as proof that cyclisation had occurred in the cold, particularly in view of the fact that iminoethers of type (IV) prepared from glycine ethyl ester are feebly basic and do not form crystalline picrates (private communication from Dr. J. W. Cornforth).

trans-4-Carbethoxy-2-phenyl-5-methyl-Δ^2-oxazoline had been prepared by cyclisation of *N*-benzoyl-*allo*threonine ethyl ester with thionyl chloride (Attenburrow *et al.*, *loc. cit.*). It was prepared by the present method in 81·5% yield and formed a picrate, m. p. 128—129°, which gave no depression in m. p.

on admixture with the picrate previously described by Attenburrow *et al.* (*loc. cit.*). It had b. p. 110—115°/10^{-2} mm., $n_D^{19°}$ 1·5272.

The configuration of the *cis*-oxazoline was confirmed as follows. The substance (2 g.) was refluxed for 4 hours with hydrobromic acid (23%; 10 ml.). The solution was cooled, diluted with water, and extracted with ether to remove benzoic acid. The aqueous layer was evaporated to dryness under reduced pressure, the syrup dissolved in hot 95% alcohol (20 ml.), and a slight excess of concentrated ammonium hydroxide added to the hot solution. *allo*Threonine crystallised out on cooling; yield 0·85 g. (79·6%). It had m. p. 248° (decomp.) and formed a benzoyl derivative, m. p. 177—178°, this m. p. being in good agreement with that recorded by West and Carter (*J. Biol. Chem.*, 1937, **119**, 113).

trans-2-*Phenyl*-5-*methyl*-Δ^2-*oxazoline*-4-*carboxylic Acid*.—The corresponding *trans*-ester (1·15 g.) was refluxed with 0·5N-sodium hydroxide (10·1 ml.) until dissolved, and then for 5 minutes longer. The solution was then evaporated to about 2 ml. in a vacuum. On scratching the vessel the *sodium* salt of the acid crystallised in rhombic plates (0·8 g.). It was recrystallised from hot water containing a small amount of sodium hydroxide; m. p. indefinite (220—240°) (Found: Na, 10·4. $C_{11}H_{10}O_3NNa$ requires Na, 10·1%). trans-2-*Phenyl*-5-*methyl*-Δ^2-*oxazoline*-4-*carboxylic acid* was obtained by adding 5N-hydrochloric acid (0·5 ml.) to a solution of the sodium salt (0·55 g.) in water (2 ml.) at 0°. After the mixture had been kept for 2 hours at 0°, the solid was filtered off, washed with a little water, and dried in a desiccator; yield 0·35 g. It had m. p. 143—144° (some decomp.) (Found: C, 64·8; H, 5·5. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4%). Hydrolysis of the *cis*-oxazoline ester in exactly the same way gave the same acid, m. p. 143—144°. A mixture of the two samples of acid had the same m. p.

O-*Benzoylthreonine*.—The oxazoline acid prepared from the *trans*-oxazoline ester (0·4 g.) was dissolved in N-hydrochloric acid (1·95 ml.; 1 equiv.) at room temperature. This gave a solution of pH 0·9. After 4 hours the solution was treated with concentrated ammonium hydroxide until no longer acid to Congo-red paper. A crystalline solid separated immediately, and after 24 hours at 0° it was collected, washed with water, and dried in a vacuum desiccator; yield 0·2 g. O-*Benzoylthreonine* formed rectangular plates from hot water, m. p. 169—170° (decomp.) It gave a positive "ninhydrin" reaction and was easily soluble in dilute hydrochloric acid (Found: N, 6·55. $C_{11}H_{13}O_4N$ requires N, 6·3%).

N-*Benzoylthreonine from the* O-*benzoyl compound*. A suspension of the *O*-benzoyl compound (0·25 g.) in water (1 ml.) was titrated with N-sodium hydroxide with rapid stirring in the presence of phenolphthalein. The end-point was reached when 1 equiv. of alkali had been added. The solution was then acidified with hydrochloric acid (Congo-red). *N*-Benzoylthreonine separated as long prisms, m. p. 146—147° (0·18 g.). It produced no depression in m. p. on admixture with an authentic specimen. The 2-phenylethylamine salt was prepared in 91% yield (see Attenburrow *et al.*, *loc. cit.*) and had m. p. 159—161°. When a sample of the oxazoline acid prepared from the *cis*-oxazoline ester was treated in the same way, the same compounds were obtained. This is further confirmation that the two samples of oxazoline acid were in fact identical. It was realised that by carrying out the changes described above in a step-wise fashion with isolation at each stage large losses resulted, thus giving no information concerning the nature of the material remaining in solution. It was found possible to prepare *N*-benzoylthreonine in 80% overall yield from either oxazoline ester when isolation of the intermediates was omitted. The way in which this was done is described below.

O-*Benzoylserine*.—4-Carbomethoxy-2-phenyl-Δ^2-oxazoline (2 g.) was heated with a solution of recrystallised barium hydroxide (3·8 g.) in water (60 ml.). The ester dissolved before the solution reached the b. p. After refluxing for 1 minute the solution was cooled and treated with 5N-sulphuric acid (*ca.* 5 ml.) until the pH was 1. After 4 hours at room temperature the excess of sulphuric acid was removed with baryta, and the precipitate washed thoroughly with boiling water. The combined filtrates, which had a pH of about 3, were evaporated to small bulk in a vacuum. The product separated as thin rectangular plates (1·4 g., 67%), easily soluble in dilute acid. After recrystallisation from hot water it had m. p. 162° (decomp.). Bergmann and Miekeley (*loc. cit.*) give m. p. 149—150° for this compound (Found: N, 6·9. Calc. for $C_{10}H_{11}O_4N$: N, 6·7%). On treatment with dilute sodium hydroxide the substance behaved exactly like *O*-benzoylthreonine and gave *N*-benzoylserine in 91% yield, m. p. 166—167°.

Large-scale Preparation of N-*Benzoylthreonine*.—Thionyl chloride was purified by distillation alternately with 2% by weight of quinoline and yellow beeswax until a colourless product resulted.

Crude ethyl α-benzamido-β-hydroxybutyrate (Attenburrow *et al.*, *loc. cit.*; 200 g.) was dissolved in chloroform (100 ml.) and dropped, with stirring, into thionyl chloride (200 ml.) cooled in an ice-bath. The temperature was kept as nearly as possible at 5—6° and addition of the ester was immediately stopped if a rise to 10° took place. The addition required about 1·5 hours. Stirring was then stopped, and the reaction mixture kept in the ice-bath for 16 hours. Melting of the ice was prevented by placing the whole apparatus in a cold room at 0°. The chloroform and excess of thionyl chloride were then removed in a vacuum at 35—38°. Without delay the dark brown, syrupy residue was poured in a thin stream into a solution of anhydrous sodium carbonate (170 g.) in water (1600 ml.) with brisk hand stirring. The solution was not allowed to become acid during this process. The amount of sodium carbonate given was usually found to be sufficient, but if not, a further addition of the solid substance was made. The emulsion of oil and water was cooled and extracted with light petroleum (b. p. 40—60°; 1000 ml. + 3 × 500 ml.). This solvent was preferred to ether because it left most of the tarry material undissolved. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue (175 g.) consisted of a mixture of the oxazolines (V*a*) and (V*b*). It was refluxed with 0·5N-sodium hydroxide (1662 ml.) until all but a small amount of tar remained undissolved. This required about 25 minutes. The brown solution was cooled and brought to pH 1 by addition of 5N-hydrochloric acid (*ca.* 335 ml.). After standing for 4 hours at room temperature, the solution was extracted four times with small portions of ether. The aqueous solution of *O*-benzoylthreonine hydrochloride so prepared was then made alkaline by addition of 5N-sodium hydroxide using phenolphthalein as indicator (externally because of the coloured solution). The solution was made just acid to litmus, treated with charcoal in the hot, filtered, evaporated under reduced pressure to a volume of about 1 l., and the charcoal treatment repeated. On acidification (Congo-red paper) with concentrated hydrochloric

acid, *N*-benzoylthreonine separated as a thick crystalline mass. The solution was kept overnight to complete the crystallisation, and the solid filtered off, washed with cold water, and dried in a desiccator; yield 145 g., m. p. 142—145°. Recrystallisation from hot water (400 ml.) gave 113 g. (63·6%, calc. on the hydroxy-ester) of pure product, m. p. 145—146° (softening from 143°). The purity was confirmed by preparation of the 2-phenylethylamine salt in 95% yield, m. p. 160—161°.

Ethyl β-Chloro-α-benzamidobutyrate.—This substance was obtained as a by-product in earlier cyclisation experiments. The following are examples. Thionyl chloride, cooled to 5° (25 ml.), was added to the crude hydroxy-ester (25 g.). The viscous ester dissolved on shaking and the temperature rapidly rose to 45°. The mixture was cooled to room temperature and kept for 4 hours. The isolation procedure was the same as above except that ether was used to extract the crude oxazoline. The ethereal extract was evaporated to small bulk (*ca.* 50 ml.) and set aside for 24 hours. *Ethyl β-chloro-α-benzamidobutyrate* crystallised out, and was filtered off and washed first with carbon tetrachloride and then with a 1 : 1 mixture of light petroleum (b. p. 40—60°) and carbon tetrachloride; yield 4·1 g., m. p. 81—83°. The material remaining in the ether after removal of the chloro-compound consisted of the corresponding oxazoline, which was purified by distillation. It appears, however, that additional impurities may have been present because the yield of the oxazoline was always considerably lower in these experiments even after allowance for the amount of chloro-compound obtained. The chloro-compound was recrystallised from alcohol–carbon tetrachloride (1 : 1) and then from alcohol and had m. p. 82—84° (Found: C, 57·6; H, 6·0. $C_{13}H_{16}O_3NCl$ requires C, 57·9; H, 6·0%).

In another experiment, carried out in a similar fashion except that the crude product was submitted to distillation without preliminary crystallisation from ether, the chloro-compound (10 g. from 169 g. of crude hydroxy-ester) crystallised slowly from the distillate. This sample, after recrystallisation, had m. p. 95—97°, mixed m. p. with the first sample 84—86° (Found: C, 58·1; H, 5·8; N, 5·2%). No doubt both these samples were mixtures containing different proportions of the two stereoisomers.

α-Benzamidocrotonic Acid and its Azlactone.—The chloro-compound (1 g.) and 2N-sodium hydroxide (15 ml.) were mixed and heated under reflux for 15 minutes. The solution was cooled, filtered, and acidified with dilute nitric acid, and the α-benzamidocrotonic acid collected. The filtrate gave a copious precipitate of silver chloride with silver nitrate solution. It was crystallised from hot water and had m. p. 192—193°; yield 0·34 g. (Found: N, 6·5. Calc. for $C_{11}H_{11}O_3N$: N, 6·8%). The crotonic acid (0·1 g.) and acetic anhydride (0·5 ml.) were boiled together for 1 minute and then evaporated under reduced pressure. The residue was crystallised from light petroleum (b. p. 40—60°). The product formed long needles, m. p. 93—95°, and gave no depression on admixture with an authentic specimen of 2-phenyl-4-ethylideneoxazol-5-one (Carter, Handler, and Melville, *loc. cit.*).

The chloro-compound (0·2 g.) was allowed to stand for 16 hours at 0° with thionyl chloride (0·5 ml.), and the mixture then evaporated to dryness under reduced pressure. By crystallisation from ligroin, unchanged starting material (0·08 g.) was recovered. The material remaining in the mother-liquors was easily soluble in ether and gave no precipitate with ethereal picric acid. It was safe to conclude that no oxazoline had been formed in this experiment.

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