The authors wish to express their grateful appreciation to Mr. Yutaka Shiraishi for his cooperation in the fermentation of *Er. ashbyii* and to Dr. Minoru Goto for his performance of bioassay with *L. casei*. Thanks are also due to members of the biochemical section of this Laboratories for their valuable advices.

Summary

The crude enzyme solution, prepared by extracting the ground mycelium of *Er. ashbyii* with a phosphate buffer and dialyzing the extract against the same buffer solution, was incubated with 6,7-dimethylribolumazine at 37°. Paper partition chromatography of the reaction mixture gave a yellow and a purple fluorescent spot. The former spot (Rf 0.3; solvent-system: EtOH·BuOH·H_2O) was cut out and extracted with hot water, and the ultraviolet spectrum of the extract was measured, showing that it is identical with that of riboflavin. The riboflavin was determined by bioassay with *L. casei* and by various chemical methods such as the lumiflavin-fluorescence method and others.

Next, investigation was made on relationship between quantity of the resulting riboflavin and reaction time, quantity of the crude enzyme solution added, and concentration of the substrate, and further on the optimal pH and temperature for the action of the enzyme solution.

Lastly, the above purple-fluorescent spot (Rf 0.23; solvent-system: EtOH·BuOH·H_2O) was proved to be that of 6-methyl-7-hydroxyribolumazine, and a new route was proposed for the formation of this compound. Further, the fact that the lumazine derivative was not affected by the crude enzyme solution made more certain the authors' previous assumption[2] that the compound is a final product in the metabolism by *Er. ashbyii*.

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123. M. Tomoeda: Studies in Stereochemistry. XX.* *dl*-Phenylserinols: A New Synthesis and its Stereochemical Findings. (7).[1] An Isomerization of *dl-threo*-2-Phenyl-4-α-hydroxybenzyl-2-oxazoline to *dl-threo*-4-Hydroxymethyl-2,5-diphenyl-2-oxazoline in Basic Media: The Correction of the Previously Proposed Structure for the Isomerization Product.

(*Pharmaceutical Institute, Medical Faculty, University of Kyushu***)

In the previous papers of this series,[2,3] it has been reported that boiling of *dl-threo*-1-phenyl-2-amino-3-bromopropyl benzoate (I) in benzene yielded nitrogen-containing colorless needles (A) in accompaniment with *dl-threo*-2-phenyl-4-α-hydroxybenzyl-2-oxazoline (II). The latter isomerized into (A) in the presence of alkali, suggesting (II) to be a precursor of (A). Furthermore, the structure of (A) has been proposed as *dl*-2-benzamido-3-phenyl-2-propen-1-ol (IIIa) or *dl*-2-benzoylimino-3-phenylpropanol (IIIb) from the result of microanalysis, molecular weight determination, infrared and ultraviolet spectral analyses, and also by the fact that on hydrogenation, (A) absorbed hydrogen to give *dl*-2-benzamido-3-phenylpropanol (IV).

* This constitutes a part of a series entitled "Studies in Stereochemistry" by T. Taguchi.
** Katakasu, Fukuoka (友枝宗光).
1) Part (6): This Bulletin, **5**, 335(1957).
2) Part (2): *Ibid.*, **4**, 80(1956).
3) Part (3): *Ibid.*, **4**, 473(1956).

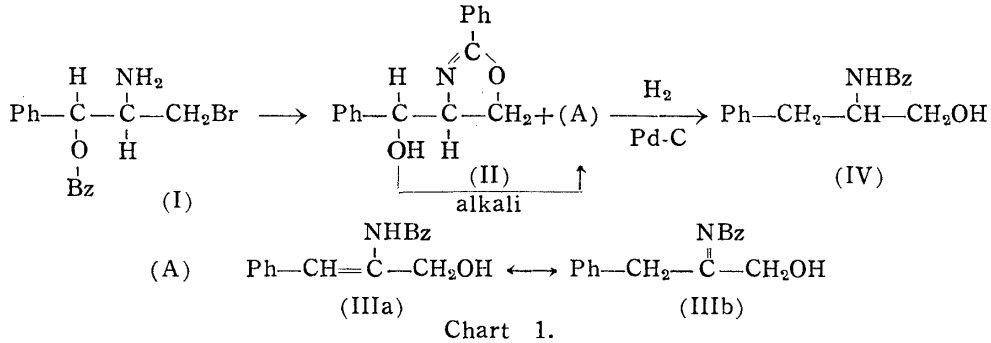

Chart 1.

Reëxamination of the structure (III)[4] was thought to be necessary, because it was doubtful that such a structure as (III) should exist so stably for acid. Thus reactions of (A) were examined again.

On heating in 1% hydrochloric acid or in hydrated ethanol with one equivalent of hydrochloric acid, (A) and its O-benzoate, derived from (A) by treatment with one equivalent of benzoyl chloride in pyridine, gave amine hydrochlorides of empirical formula $C_{16}H_{17}NO_3 \cdot HCl$ and $C_{23}H_{21}NO_4 \cdot HCl$, respectively. The former hydrochloride was identified as *dl-threo*-2-amino-3-benzoyloxy-3-phenylpropanol (V) hydrochloride[2] and the latter, as hydrochloride of *dl-threo*-1-phenyl-2-amino-1,3-propanediol dibenzoate (VI)[5] by mixed m.p. determinations. On treatment with alkali, the hydrochlorides of (V) and (VI) gave *dl-threo*-1-phenyl-2-benzamido-1,3-propanediol (VII)[1] and *dl-threo*-1-phenyl-2-benzamido-3-benzoyloxypropanol (VIII)[5], respectively, which fact provides further support for the structure of these amines. The results observed above can not be compatible with the previously proposed structure (IIIa or IIIb), since such structures are known to be unstable for acid to be hydrolyzed into ketone.[6]

There are two possible structures, *dl*-1-benzoyl-2-hydroxymethyl-3-phenylaziridine (IX) and *dl*-2,5-diphenyl-4-hydroxymethyl-2-oxazoline (X), for the empirical formula of (A), $C_{16}H_{15}NO_2$, which is consistent with the observations. The O-benzoate (XI) of the oxazo-

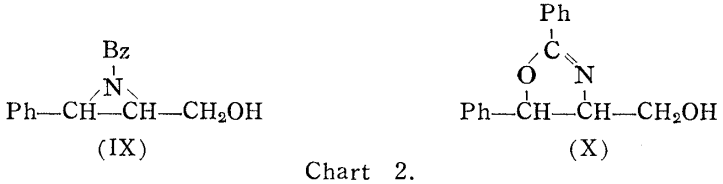

Chart 2.

line (X) was successfully synthesized from *dl-threo*-1-phenyl-2-amino-3-benzoyloxypropanol (XII) hydrochloride[2] and ethyl benzimidate, and was proved to be identical with the O-benzoate of (A) by a mixed m.p. determination. (X) of *threo* configuration[7] derived from its O-benzoate (XI) by hydrolysis with sodium hydroxide was also identical with (A). The oxazoline (X) was directly obtained by condensation of *dl-threo*-1-phenyl-2-amino-1,3-propanediol (XIII) hydrochloride, derived from *dl-threo*-2-amino-3-chloro-3-phenylpropanol (XIV) hydrochloride[8] by solvolysis in water, and ethyl benzimidate, proving preference of the oxazoline-ring formation at C-1 and C-2 of (XIII). The structures and *threo* configuration of (X) and (XI) were supported by infrared spectra and the common knowledge that con-

4) Alberti, *et al.* reported synthesis of this compound by treatment of 2-benzamido-3-chloro-3-phenylpropyl benzoate with alkali (Gazz. chim. ital., **82**, 53(1952)), but it was not obtained in the present tracing of their procedure.
5) T. Taguchi, M. Tomoeda, T. Ishida: Yakugaku Zasshi, **75**, 666(1955).
6) a) M. Svoboda, *et al.*: Collection Czechoslov. Chem. Communs., **19**, 545(1954); b) J. Kollonitsch, *et al.*: Chem. & Ind. (London), **1955**, 38.
7) U. S. Pat. 2,562,114 (1951).
8) S. Ikuma, *et al.*: Yakugaku Zasshi, **72**, 310(1952).

densations of epimeric amino alcohols and alkyl benzimidate give oxazolines with retention.[7, 9] On the other hand, with a view to proving the difference in (A) and (IX), a synthesis of (IX) from the hydrochloride of *dl-threo*-2-amino-3-chloro-3-phenylpropanol (XIV) or *dl-threo*-2-amino-3-bromo-3-phenylpropyl benzoate (XV)[10] with alkali[11] was tried but it failed, causing elimination to give an oily unsaturated product.

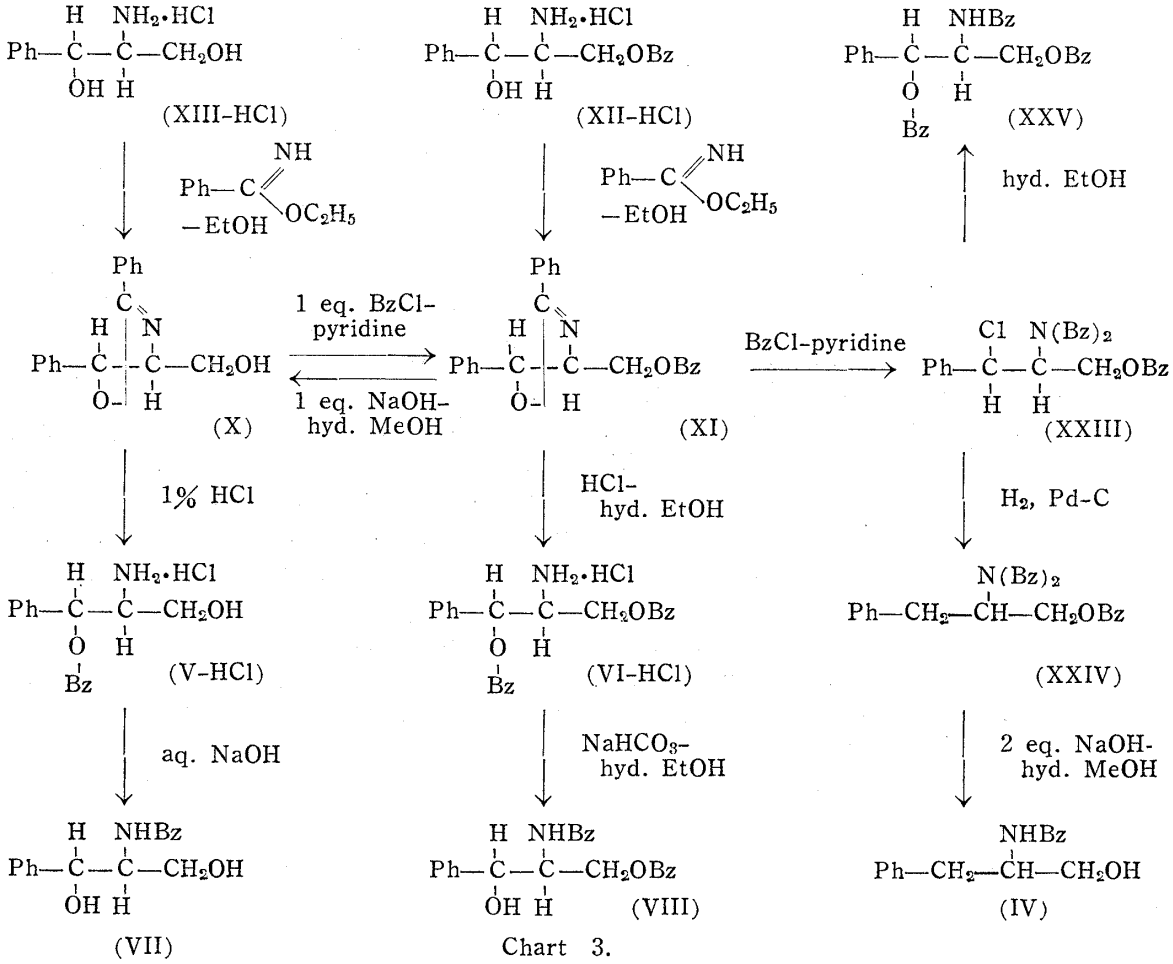

Chart 3.

Considering all the observations gained hereto, it is evident that an isomerization of the initially produced oxazoline (II) to the oxazoline (X) with retention occurred during the treatment of (II) in alkaline media, but reactions of the oxazoline (X) and its derivatives were investigated further to add proof to the stereospecificity of the isomerization and gain new informations on their chemical behavior.

It seemed of value to seek analogous phenomenon in a series of optically active *p*-nitro analogs. The treatment of L-*threo*-1-*p*-nitrophenyl-2-benzamido-1,3-propanediol (XVI)[12]

9) a) D. F. Elliot: J. Chem. Soc., **1949**, 589; b) W. S. Johnson: J. Am. Chem. Soc., **72**, 2187(1950); c) E. Hoffmann: Swiss Pat. 283,587 (1951); d) S. Ikuma, *et al.*: Yakugaku Zasshi, **72**, 950 (1952); e) S. Ikuma, *et al.*: *Ibid.*, **72**, 957(1952); f) M. Viscontini, *et al.*: Helv. Chim. Acta, **36**, 1(1953); g) R. Slack, *et al.*: Brit. Pat. 698,542 (1953); h) H. Adkins, *et al.*: J. Am. Chem. Soc., **76**, 147(1954).

10) Part 1: J. Am. Chem. Soc., **78**, 1468 (1956).

11) Alkaline treatment of the hydrochloride of *dl-threo*-1-chloro-1-phenyl-2-aminopropane resulted in the formation of *dl-erythro*-2-phenyl-3-methylaziridine (K. Tanaka: Yakugaku Zasshi, **70**, 212 (1950)).

12) A. M. Crooks, *et al.*: U.S.Pat. 2,483,855(1949).

with *p*-toluenesulfonyl chloride in pyridine[13] gave L-*threo*-4-(*p*-nitro-α-hydroxybenzyl)-2-phenyl-2-oxazoline (XVII)[14] which on hydrolysis with hydrochloric acid in hydrated methanol afforded L-*threo*-1-*p*-nitrophenyl-2-amino-3-benzoyloxypropanol (XVIII) hydrochloride.[14] When the oxazoline (XVII) was boiled in hydrated ethanol with potassium acetate, a hydroxy compound, m.p. 222~224°, of the same empirical formula as that of (XVII) was formed. The compound gave, on treatment with one equivalent of benzoyl chloride in pyridine, an O-benzoate which was proved to be identical with L-*threo*-2-phenyl-4-benzoyloxymethyl-5-*p*-nitrophenyl-2-oxazoline (XIX)[14] derived from L-*erythro*-1-*p*-nitrophenyl-2-benzamido-3-benzoyloxypropanol (XX)[15] after successive treatments with thionyl chloride and aqueous sodium hydrogen carbonate solution.[16]

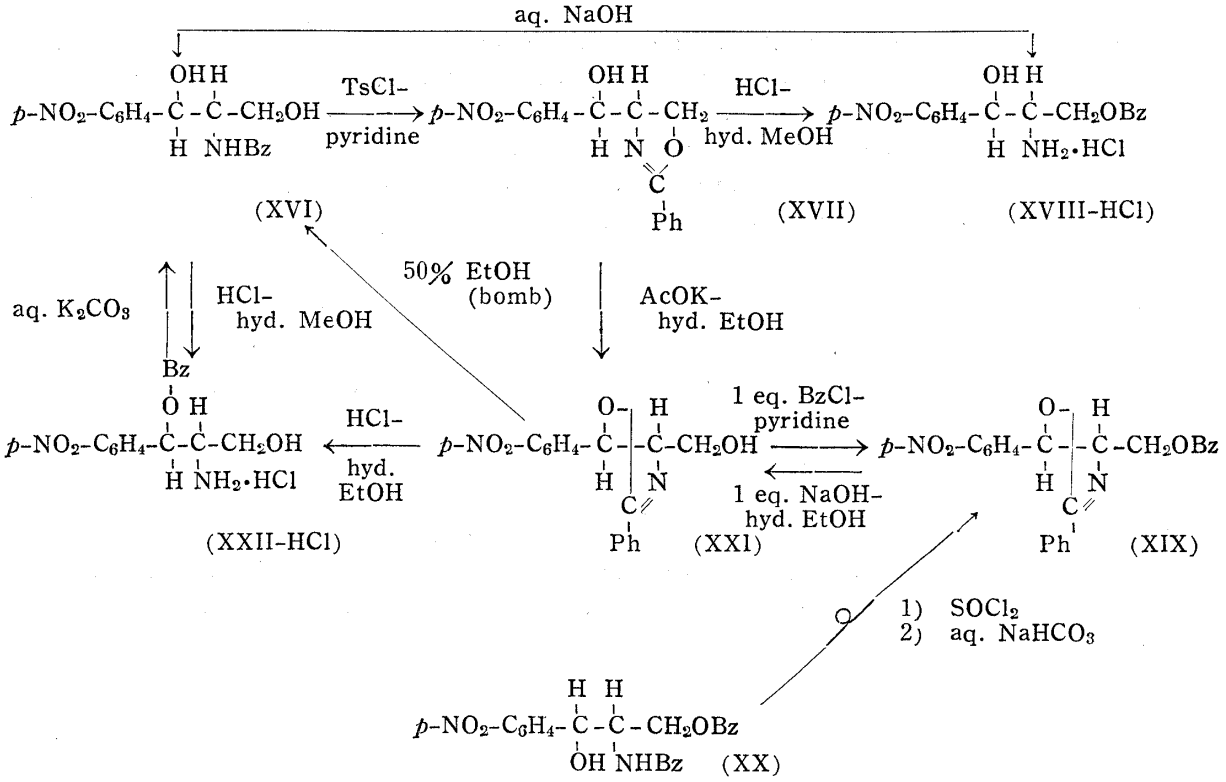

Chart 4.

Further, alkaline hydrolysis of (XIX) derived from (XX) with one equivalent of sodium hydroxide in the cold gave L-*threo*-2-phenyl-4-hydroxymethyl-5-*p*-nitrophenyl-2-oxazoline (XXI)[7,14] which was identical with the product of m.p. 222~224°; the structures of (XIX) and (XXI) were confirmed by their infrared spectra and the fact that the hydrolysis of (XXI) with hydrochloric acid in hot hydrated ethanol gave L-*threo*-2-amino-3-benzoyloxy-3-*p*-nitrophenylpropanol (XXII) hydrochloride[14] which was identical with an authentic specimen derived from (XVI) after N→O acyl migration. Besides, (XXI) afforded the N-benzoate (XVI) by heating in 50% ethanol under pressure showing the usual ring opening manner of oxazoline.

An interesting finding was the benzoylation of the oxazoline (X). As has been mentioned, (X) gave its O-benzoate (XI) on treatment with one equivalent of benzoyl chloride

13) On similar treatment, D-*threo*-1-*p*-nitrophenyl-2-dichloracetamido-1,3-propanediol gave D-*threo*-2-dichloromethyl-4-(*p*-nitro-α-hydroxybenzyl-)2-oxazoline (L. Almirante, *et al.*: Il Farmaco (Pavia) Ed. sci., **10**, 3(1955)).
14) C. G. Alberti, *et al.*: Gazz. chim. ital., **85**, 324(1955).
15) G. W. Moersch, *et al.*: J. Am. Chem. Soc., **76**, 1703(1954).
16) Analogous ring closure of oxazolines is shown in the following cases a)(8); b)(9d).

in pyridine in a good yield. The treatment of (X) with more than one equivalent of benzoyl chloride in pyridine, however, gave chlorine-containing crystals in accompaniment with (XI). Since the empirical formula of these crystals showed an addition of one molecule of benzoyl chloride to the O-benzoate (XI) of the oxazoline (X), and its infrared spectrum showed the existence of diacylamide structure, the structure and configuration in question were proposed as *dl-erythro*-2-dibenzamido-3-chloro-3-phenylpropyl benzoate (XXIII). On hydrogenation, (XXIII) absorbed one equivalent of hydrogen to give *dl*-2-dibenzamido-3-phenylpropyl benzoate (XXIV), which was then converted into (IV) after mild alkaline hydrolysis; these are proofs for the structure of (XXIII). Furthermore, (XXIII) was boiled in hydrated ethanol for a short time to give *dl-threo*-1-phenyl-2-benzamido-1,3-propanediol dibenzoate (XXV),[17] in excellent yield accompanying Walden inversion which also confirms the *erythro* assignment for (XXIII).

It seems unusual for generally accepted properties of oxazoline that (X) showed the following behavior, at two points: First, saturation of the dehydrated ethanolic solution of (X) with dry hydrogen chloride resulted in recovery of about one-half the amount of (X) used. However, as Svoboda, *et al.*[6a] has pointed out on the relatively stable character of the oxazoline of (B) type to acid compared with that of (C) type, the basicity of (X) might be unusually weak and stable to acids, not causing an easy ring opening.[18]

Chart 5.

Second, (X) and its O-benzoate (XI) absorbed hydrogen to give acylamide compounds, (IV) and its O-benzoate (XXVI),[17] respectively, and it may well be understood by analogy with the fact that hydroxyl group α to the aromatic ring is reduced by catalytic hydrogenation.[19]

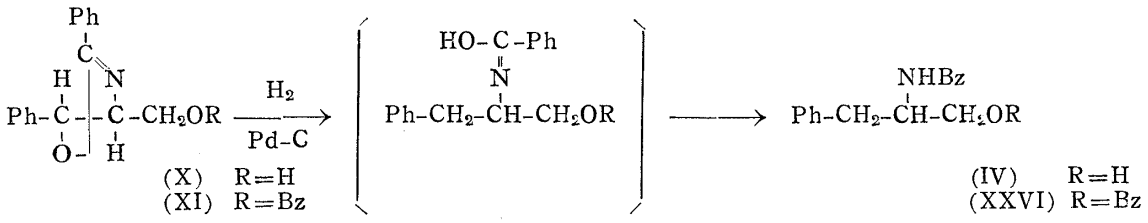

Chart 6.

With respect to the possible mechanism of isomerization reaction from the oxazoline of (C) type to that of (B) type, it is presumed that the isomerization or rearrangement proceeds via completely stereospecific course without Walden inversion, as shown in Chart 7. The explanation given to the retention mechanism of acyl migration in a series of 2-acylamino alcohols by Welsh[20] would support the present experimental facts. Besides, Alberti, *et al.*[14] hold the same view that (XVII) isomerized to (XXI) at melting point, the mechanism

17) Part 5: This Bulletin, **5**, 189(1957).
18) Alberti, *et al.*[14] reported a successful isolation of the hydrochloride of (XXI) from its dioxane solution.
19) a) A. Skita, *et al.*: Ber., **45**, 3579(1912); b) L.I. Smith, *et al.*: J. Am. Chem. Soc., **62**, 2641 (1940); c) L.I. Smith, *et al.*: J. Am. Chem. Soc., **70**, 2209(1948).
20) L.H. Welsh: J. Am. Chem. Soc., **71**, 3500(1949).

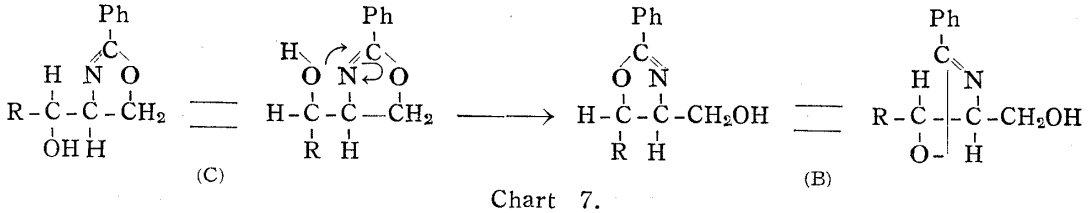

Chart 7.

of which might be the same. It is due to the catalytic action of alkali that the isomerization took place at a much lower temperature than the Alberti's in the present case.

The writer expresses thanks to Prof. Taguchi for his kind advice and encouragement through the course of this work. His thanks are also due to the members of the Microanalytical Center of this University and of the Microanalytical Room of this Institute for the microanalyses, to Dr. Ueda and Mr. Yano, and also to the Sankyo Co. for the infrared spectral determination, and to the Sankyo Co. for supplying L-*threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol.

Experimental

***dl-threo*-2,5-Diphenyl-4-hydroxymethyl-2-oxazoline (X)**—a) From *dl-threo*-2,5-Diphenyl-4-benzoyloxymethyl-2-oxazoline (XI) derived from *dl-threo*-1-Phenyl-2-amino-3-benzoyloxypropanol (XII) Hydrochloride: A solution of 29.0 mg. of (XI) in a mixture of 2.23 mg. of NaOH and 10 cc. of 95% MeOH was boiled for 2 hrs. and on cooling, crystals deposited. Recrystallization from benzene gave colorless needles, m.p. 159~160°, alone and on admixture with a sample of the isomerization product[3]; yield, 19.8 mg. *Anal.* Calcd. for $C_{16}H_{15}O_2N$ (X): C, 75.87; H, 5.97; N, 5.53. Found: C, 75.73; H, 5.98; N, 5.77. I.R. λ_{max}^{Nujol} 3.08μ(OH), 6.09μ(C=N). The infrared spectrum of the isomerization product[3] was taken under the same condition: I.R. λ_{max}^{Nujol} 3.08μ(OH), 6.09μ(C=N).

b) From *dl-threo*-2-Amino-3-chloro-3-phenylpropanol (XIV) Hydrochloride[8] via *dl-threo*-1-Phenyl-2-Amino-1,3-propanediol (XIII) Hydrochloride: A solution of 500 mg. of (XIV-HCl) in 50 cc. of H_2O was boiled for 2 hrs.; the pH of the solution changed from 5.0 to 1.8. The solution was concentrated and dried over NaOH *in vacuo* to give an oily product (XIII-HCl). The oil was dissolved in 15 cc. of EtOH, to which 370 mg. of ethyl benzimidate was added, and the solution was stirred for 1 day at room temperature and concentrated *in vacuo* to give a solid. The solid was extracted with AcOEt and the AcOEt solution was washed with satd. $NaHCO_3$ solution, dried over anhyd. Na_2SO_4, and concentrated to a small volume. Upon addition of ether crystals deposited, m.p. 153~159°; wt., 290 mg. Recrystallization from benzene gave colorless needles, m.p. 158~160°, which did not depress the m.p. of a sample of (X) obtained by procedure (a) and of the isomerization product.[3]

Concentration of the ethereal mother liquor gave prisms, m.p. 100~120°; wt., 25 mg. This was assumed to be crude *dl-threo*-2-phenyl-4-α-hydroxybenzyl-2-oxazoline, but its further characterization failed.

Treatment of (X) in dehyd. EtOH saturated with dry Hydrogen Chloride—A solution of 300 mg. of (X) in 20 cc. of dehyd. EtOH was saturated with dry HCl at 0° and kept in the cold for 2 days, followed by concentration *in vacuo* to give a solid residue. The residue was treated with a mixture of AcOEt and H_2O, and the AcOEt layer was dried over anhyd. Na_2SO_4, concentrated *in vacuo*, and on addition of ether colorless needles deposited, m.p. 157~160°; yield, 145 mg. After crystallization from benzene, it melted at 158~160°, alone and on admixture with a sample of (X) described above.

Concentration of the H_2O layer *in vacuo* and addition of a mixture of acetone and ether deposited colorless needles, m.p. 190~193°(decomp.), alone and on admixture with an authentic sample of *dl-threo*-2-amino-3-benzoyloxy-3-phenylpropanol (V) hydrochloride[2]; yield, 105 mg. Picrate: Recrystallization from 50% EtOH gave yellow prisms, m.p. 177~179°, alone and on admixture with an authentic sample of (V) picrate.[2]

***dl-threo*-2,5-Diphenyl-4-benzoyloxymethyl-2-oxazoline (XI)**—a) From (X): A mixture of 1.5 g. of (X) in 10 cc. of pyridine was treated with 925 mg. of BzCl for several hrs. in the cold and the reaction mixture was poured into ice water to deposit a solid. Recrystallization from petroleum ether gave colorless needles, m.p. 94~98°, alone and on admixture with a sample of (XI) obtained by procedure (b); yield, 1.590 mg. *Anal.* Calcd. for $C_{23}H_{19}O_3N$ (XI): C, 77.29; H, 5.35; N, 3.92. Found: C, 77.68; H, 5.41; N, 3.86. I.R. λ_{max}^{Nujol} 5.85μ(C_6H_5COO); 6.05μ(C=N).

b) From *dl-threo*-1-Phenyl-2-amino-3-benzoyloxypropanol (XII) Hydrochloride[2]: To a solution of 305 mg. of (XII-HCl) in 5 cc. of EtOH, 150 mg. of ethyl benzimidate in 5 cc. of EtOH was added and the solution was kept stirring for 2 days at room temperature. Concentration *in vacuo* and addition of H_2O deposited crystals, m.p. 94~97°; yield, 145 mg. Recrystallization from petr. ether gave colorless needles, m.p. 97~99°. *Anal.* Calcd. for $C_{23}H_{19}O_3N$ (XI): C, 77.29; H, 5.35; N, 3.92. Found:

C, 77.60; H, 5.52; N, 3.89. I.R. λ_{max}^{Nujol} 5.83μ(C_6H_5COO); 6.06μ(C=N).

Catalytic Hydrogenation of (XI) to *dl*-2-Benzamido-3-phenylpropyl Benzoate (XXVI)—A solution of 36.6 mg. of (XI) in 35 cc. of MeOH was hydrogenated under atmospheric pressure using a catalyst prepared from 100 mg. of carbon and 1 cc. of 1% $PdCl_2$, and 3.4 cc. of H_2 was absorbed at 21° in 2 mins. After filtration, the filtrate was concentrated *in vacuo* and the deposited solid was recrystallized from EtOH to colorless needles, m.p. 150~151°, alone and on admixture with an authentic sample of (XXVI).[17] *Anal.* Calcd. for $C_{23}H_{21}O_3N$ (XXVI): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.81; H, 5.88; N, 3.58.

***dl-threo*-2-Amino-3-benzoyloxy-3-phenylpropanol (V) Hydrochloride**—A solution of 600 mg. of (X) in 50 cc. of 1% HCl was boiled for 2 hrs. and concentrated *in vacuo* to give a solid. Recrystallization from a mixture of MeOH and acetone gave colorless needles, m.p. 191~193°(decomp.), alone and on admixture with an authentic sample of (V-HCl)[2]; yield, 480 mg. *Anal.* Calcd. for $C_{16}H_{17}O_3N \cdot HCl$ (V-HCl): C, 62.43; H, 5.89; N, 4.55. Found: C, 62.26; H, 5.83; N. 4.52. Picrate: To an aqueous solution of the hydrochloride, satd. sodium picrate solution was added and yellow crystals deposited. Recrystallization from 80% EtOH gave yellow prisms, m.p. 175~178°, alone and on admixture with an authentic sample of (V-picrate).[2]

***dl-threo*-1-Phenyl-2-amino-1, 3-propanediol Dibenzoate (VI) Hydrochloride**—A solution of 200 mg. of (XI) in a mixture of 0.23 cc. of 10% HCl and 20 cc. of 50% EtOH was boiled for 2 hrs. and concentrated *in vacuo* to give a solid, m.p. 186~189°; yield, 210 mg. Recrystallization from acetone gave colorless needles, m.p. 187~189°, alone and on admixture with an authentic sample of (VI-HCl).[5] *Anal.* Calcd. for $C_{23}H_{21}O_4N \cdot HCl$ (VI-HCl): C, 67.15; H, 5.35; N, 3.41. Found: C, 67.23; H, 5.60; N, 3.23.

A solution of 210 mg. of the hydrochloride in 40 cc. of 50% EtOH was made alkaline with satd. $NaHCO_3$ solution to deposit crystals gradually. After 2 days, crystals were collected (wt., 145 mg.) and recrystallized from AcOEt to colorless needles, m.p. 146~148°, alone and on admixture with an authentic sample of *dl-threo*-1-phenyl-2-benzamido-3-benzoyloxypropanol (VIII)[5]; yield, 110 mg.

***dl-threo*-1-Phenyl-2-benzamido-1,3-propanediol** (VII)—A solution of 60 mg. of (V-HCl) in 2 cc. of H_2O was made alkaline with a few drops of 10% NaOH to deposit an oil, which solidified. Recrystallization from AcOEt gave colorless needles, m.p. 162~164°, alone and on admixture with an authentic sample of (VII)[1]; yield, 50 mg. *Anal.* Calcd. for $C_{16}H_{17}O_3N$ (VII): C, 70.83; H, 6.32; N, 5.16. Found: C, 70,87; H, 6.75; N, 5.33.

***dl-erythro*-2-Dibenzamido-3-chloro-3-phenylpropyl Benzoate (XXIII)**—a) From (X) with the formation of (XI): To a solution of 450 mg. of (X) in 5 cc. of pyridine, 540 mg. of BzCl was added in the cold. The reaction mixture was kept overnight at room temperature, poured into ice water, and crystals deposited, m.p. 60~110°; wt., 700 mg. The crystals (500 mg.) were treated with petr. ether and the remaining needles were recrystallized from EtOH to colorless needles, m.p. 192~194°, alone and on admixture with an authentic sample of *dl-threo*-1-phenyl-2-benzamido-1, 3-propanediol dibenzoate (XXV)[17]; yield, 40 mg.

Concentration of the petr. ether mother liquor gave two kinds of crystals, colorless prisms and needles. The prisms, after recrystallization from petr. ether, melted at 128~130°; yield, 165 mg. *Anal.* Calcd. for $C_{30}H_{24}O_4NCl$ (XXIII): C, 72.36; H, 4.86; N, 2.81. Found: C, 71.91; H, 5.01; N, 3.07. I.R. λ_{max}^{Nujol} 5.74μ(C_6H_5COO); 5.88, 6.01μ($(C_6H_5CO)_2N$).

The colorless needles, after recrystallization from petr. ether, melted at 93~96°, alone and on admixture with a sample of (XI) described above; yield, 250 mg.

Further concentration of the petr. ether mother liquor gave a solid, m.p. 140~160°, weighing 10 mg., the characterization of which failed.

b) From (XI): One g. of (XI) in 10 cc. of pyridine was treated with 1.0 g. of BzCl for 3 days at room temperature. The brown solution was poured into ice water to deposit an oily product. This was extracted with AcOEt, which was washed with dil. HCl, satd. $NaHCO_3$, and H_2O, and dried over anhyd. Na_2SO_4. After filtration, the solution was concentrated *in vacuo* and on addition of a mixture of ether and petr. ether crystals deposited. Recrystallization from ether gave colorless prisms, m.p. 129~131°, alone and on admixture with a sample of (XXIII) obtained by procedure (a); yield, 630 mg.

Concentration of the ethereal mother liquor gave a crude material (XI), m.p. 94~101°; yield, 155 mg.

***dl*-2-Dibenzoylamino-3-phenylpropyl Benzoate (XXIV)**—A solution of 50 mg. of (XXIII) in 10 cc. of AcOEt was hydrogenated under atmospheric pressure using a catalyst prepared from 100 mg. of carbon and 0.5 cc. of 1% $PdCl_2$ and 2.5 cc. of hydrogen was absorbed at 14°. After filtration, the solution was concentrated *in vacuo* and on addition of ether crystals deposited, m.p. 146~151°; yield, 30 mg. Recrystallization from ether gave colorless needles, m.p. 151~153°. *Anal.* Calcd. for $C_{30}H_{25}O_4N$ (XXIV): C, 77.71; H, 5.44; N, 3.02. Found: C, 77.79; H, 5.45; N, 2.91. I.R. λ_{max}^{Nujol} 5.84μ(C_6H_5COO); 5.94, 6.08μ($(C_6H_5CO)_2N$).

A solution of 50 mg. of (XXIV), obtained above, in a mixture of 11 mg. of NaOH and 7.4 cc. of 90% MeOH was boiled for 1 hr., and concentrated *in vacuo* to give crystals, m.p. 145~148°; yield, 25 mg. Recrystallization from AcOEt gave colorless needles, m.p. 148~150°, alone and on admixture with an authentic sample of (IV).[3]

***dl-threo*-1-Phenyl-2-benzamido-1,3-propanediol Dibenzoate (XXV)**—A solution of 26.2 mg. of (XXIII) in 5 cc. of 95% EtOH was boiled for 1 hr. and after cooling, colorless needles deposited, m.p. 193~195°, alone and on admixture with an authentic sample of (XXV)[17]; yield, 20.2 mg. *Anal.* Calcd. for $C_{30}H_{25}O_5N$ (XXV): C, 75.13; H, 5.27; N, 2.92. Found: C, 75.08; H, 5.26; N, 3.24. I.R. λ_{max}^{Nujol} 2.95μ(NH); 5.81μ(C_6H_5COO); 6.09μ(Amide I); 6.52μ(Amide II).

Concentration of the EtOH mother liquor gave 2.5 mg. of crystals, m.p. 177~188°, and recrystallization from EtOH gave pure (XXV), m.p. 193~195°.

L-*threo*-2-Phenyl-4-(*p*-nitro-α-hydroxybenzyl)-2-oxazoline (XVII)—To a solution of 500 mg. of L-*threo*-1-(*p*-nitrophenyl)-2-benzamido-1,3-propanediol (XVI)[12] in 5 cc. of pyridine, 300 mg. of *p*-toluenesulfonyl chloride was added in the cold and the solution was kept overnight at room temperature. The reaction mixture was poured into ice water to deposit a solid, which was filtered, washed with satd. $NaHCO_3$ and H_2O, m.p. 152~156°; wt., 370 mg. Recrystallization from AcOEt gave pale yellow needles, m.p. 165~167°.[14] *Anal.* Calcd. for $C_{16}H_{14}O_4N_2$ (XVII): C, 64.42; H, 4.73; N, 9.39. Found: C, 64.55; H, 4.77; N. 9.18. $[\alpha]_D^{12}$ +64.8° (c=0.987 in dioxane). I.R. λ_{max}^{Nujol} 3.13μ(OH); 6.09μ(C=N); 6.57, 7.43μ(*p*-NO_2-C_6H_4).

L-*threo*-1-*p*-Nitrophenyl-2-amino-3-benzoyloxypropanol (XVIII) Hydrochloride—A solution of 600 mg. of (XVII) in a mixture of 1.2 cc. of 10% HCl and 60 cc. of 90% MeOH was boiled for a short time, stood overnight at room temperature, concentrated *in vacuo*, and on addition of ether crystals deposited. Recrystallization from a mixture of MeOH and ether gave colorless prisms, m.p. 203~205° (decomp.)[14]; yield, 690 mg. *Anal.* Calcd. for $C_{16}H_{16}O_5N_2$·HCl (XVIII-HCl): C, 54.47; H, 4.86; N, 7.94. Found: C, 54.81; H, 5.08; N, 7.86. $[\alpha]_D^{19}$ -49.4° (c=1.72 in MeOH).

An aqueous solution of the hydrochloride was made alkaline with NaOH to give pale yellow needles, m.p. 170~172°, alone and on admixture with an authentic sample of (XVI).[12]

L-*threo*-2-Phenyl-4-benzoyloxymethyl-5-*p*-nitrophenyl-2-oxazoline (XIX)—a) From L-*erythro*-1-*p*-nitrophenyl-2-benzamido-3-benzoyloxypropanol (XX)[15]: Two hundred mg. of (XX) was added in small portions to 1 cc. of $SOCl_2$ and the reaction mixture was allowed to stand for 3 hrs.; the whole treatment was carried out in the cold. After addition of a mixture of $CHCl_3$ and AcOEt, the solution was washed with satd. $NaHCO_3$, dried over anhyd. Na_2SO_4, and concentrated *in vacuo* to give a solid. Recrystallization from MeOH gave pale yellow leaflets, m.p. 154~156.5°[14]; yield, 145 mg. *Anal.* Calcd. for $C_{23}H_{18}O_5N_2$ (XIX): C, 68.65; H, 4.50; N, 6.96. Found: C, 69.06; H, 4.46; N, 7.14. $[\alpha]_D^{24}$+75.9° (c=0.725 in dioxane). I.R. λ_{max}^{Nujol} 5.81μ(C_6H_5COO); 6.08μ(C=N); 6.55, 7.38μ(*p*-NO_2-C_6H_4).

b) From L-*threo*-2-Phenyl-4-hydroxymethyl-5-*p*-nitrophenyl-2-oxazoline (XXI): To a solution of 500 mg. of (XXI) in 5 cc. of pyridine, 260 mg. of BzCl was added in the cold. The reaction mixture was kept overnight at room temperature and poured into ice water to deposit a solid, m.p. 146~152°; wt., 660 mg. Recrystallization from MeOH gave yellow leaflets, m.p. 154~156°, alone and on admixture with a sample of (XIX) obtained by procedure (a); yield, 380 mg. *Anal.* Calcd. for $C_{23}H_{18}O_5N_2$ (XIX): C, 68.65; H, 4.50; N, 6.96. Found: C, 68.39; H, 4.62; N, 6.80. $[\alpha]_D^{12}$ +76.8° (c=0.899, in dioxane). I.R. λ_{max}^{Nujol} 5.83μ(C_6H_5COO); 6.10μ(C=N); 6.58, 7.40μ(*p*-NO_2-C_6H_4).

L-*threo*-2-Phenyl-4-hydroxymethyl-5-*p*-nitrophenyl-2-oxazoline (XXI)—a) From (XVII): A solution of 200 mg. of (XVII) in a mixture of 200 mg. of anhyd. AcOK and 20 cc. of 90% EtOH was boiled for 20 hrs., concentrated *in vacuo*, and on addition of H_2O pale yellow crystals deposited, m.p. 216°; wt., 185 mg. Recrystallization from MeOH gave pale yellow needles, m.p. 223~225°,[7,14] alone and on admixture with a sample of (XXI) obtained by procedure (b). *Anal.* Calcd. for $C_{16}H_{14}O_4N_2$ (XXI): C, 64.42; H, 4.73; N, 9.39. Found: C, 64.57; H, 4.90; N, 9.20. $[\alpha]_D^{12}$ +199.0° (c=0.502, in dioxane). I.R. λ_{max}^{Nujol} 3.09μ(OH); 6.08μ(C=N); 6.55, 7.35μ(*p*-NO_2-C_6H_4).

b) From (XIX) derived from (XX): To a solution of 100 mg. of (XIX) in 18 cc. of EtOH, 11 mg. of NaOH in 2 cc. of H_2O was added at room temperature and pale yellow needles deposited gradually. The needles were collected after 3 hrs., m.p. 221~224°; yield, 50 mg. *Anal.* Calcd. for $C_{16}H_{14}O_4N_2$ (XXI): C, 64.42; H, 4.73; N, 9.39. Found: C, 64.39; H, 4.72; N. 8.96. $[\alpha]_D^{24}$ +200.7° (c=0.588, in dioxane). I.R. λ_{max}^{Nujol} 3.11μ(OH); 6.10μ(C=N); 6.55, 7.37μ(*p*-NO_2-C_6H_4).

Concentration of the EtOH mother liquor gave crude (XXI), m.p. 217~223°; wt., 20 mg.

L-*threo*-2-Amino-3-benzoyloxy-3-*p*-nitrophenylpropanol (XXII) Hydrochloride—a) From (XVI): A solution of 1.0 g. of (XVI) in 80 cc. of 90% MeOH containing 1% HCl was kept overnight at room temperature, followed by concentration *in vacuo* to give crystals, m.p. 197~202° (decomp.); yield, 700 mg. Recrystallization from dehyd. EtOH gave colorless prisms, m.p. 202~205° (decomp.).[14] *Anal.* Calcd. for $C_{16}H_{16}O_5N_2$·HCl (XXII-HCl): C, 54.47; H, 4.86; N, 7.94. Found: C, 54.70; H, 5.08; N, 8.10. $[\alpha]_D^{18}$ -63.0° (c=0.98, in MeOH).

A hot solution of 280 mg. of the hydrochloride in H_2O was made alkaline with K_2CO_3 to give an oily product which then crystallized, m.p. 164~168°; wt., 235 mg. Recrystallization from AcOEt gave pale yellow needles, m.p. 171°, alone and on admixture with an authentic sample of (XVI)[12]; yield, 175 mg. *Anal.* Calcd. for $C_{16}H_{16}O_5N_2$ (XVI): N, 8.86. Found: N, 8.78.

b) From (XXI): A solution of 1.0 g. of (XXI) in a mixture of 1.3 cc. of 10% HCl and 180 cc. of EtOH was boiled for 2 hrs. and concentrated *in vacuo* to give a solid, m.p. 198~202° (decomp.). Recrystallization from EtOH gave colorless prisms, m.p. 202~204° (decomp.),[14] alone and on admixture with a sample of (XXII-HCl) obtained by procedure (a); yield, 760 mg. *Anal.* Calcd. for $C_{16}H_{16}O_5N_2 \cdot HCl$ (XXII-HCl): C, 54.47; H, 4.86; N, 7.94. Found: C, 54.42; H, 5.02; N, 8.08. $[\alpha]_D^{18}$ −63.1° (c=0.49 in MeOH).

L-*threo*-1-*p*-Nitrophenyl-2-benzamido-1,3-propanediol (XVI)—a) From (XXI): A solution of 150 mg. of (XXI) in 3 cc. of 50% EtOH was heated at 120° for 3 hrs., and then at 160° for 11 hrs. under pressure. After cool, the brown solution was treated with carbon and the decolorized filtrate was concentrated *in vacuo* to give a solid, which was washed with 3 cc. of 10% HCl, m.p. 147~165°; wt., 95 mg. Recrystallization from AcOEt gave pale yellow needles, m.p. 168~171°, alone and on admixture with an authentic sample of (XVI)[12]; yield, 40 mg. $[\alpha]_D^{13}$ +120.3° (c=0.316 in MeOH).

b) From (XXII-HCl) derived from (XXI): A solution of 200 mg. of (XXII-HCl) in H_2O was made alkaline with K_2CO_3 to give an oily product, which then crystallized, m.p. 168~171°; yield, 150 mg. Recrystallization from AcOEt gave pale yellow needles, m.p. 170~172°, alone and on admixture with an authentic sample of (XVI).[12] *Anal.* Calcd. for $C_{16}H_{16}O_5N_2$ (XVI): C, 60.75; H, 5.10; N, 8.86. Found: C, 60.84; H, 5.30; N, 9.03. $[\alpha]_D^{17}$ +121.0° (c=0.777 in MeOH).

Summary

In the preceding paper of this series, it was tentatively assumed, while leaving some doubt, that *dl-threo*-2-phenyl-4-α-hydroxybenzyl-2-oxazoline isomerized into *dl*-2-benzamido-3-phenyl-2-propen-1-ol or *dl*-2-benzimido-3-phenylpropanol in basic media. In this paper, the structure of the isomerization product was corrected to *dl-threo*-2,5-diphenyl-4-hydroxymethyl-2-oxazoline by reëxamination of chemical properties and final synthesis. The analogous isomerization observed in the optically active *p*-nitro analogs is a further support for the correction and a possible mechanism of the isomerization without Walden inversion was proposed. *dl-threo*-2,5-Diphenyl-4-benzoyloxymethyl-2-oxazoline was found to add benzoyl chloride causing ring opening with Walden inversion to give *dl-erythro*-2-dibenzoylamino-3-chloro-3-phenylpropyl benzoate.

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