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61. Munemitsu Tomoeda : Studies in Stereochemistry. XIV.* *dl*-Phenylserinols : A New Synthesis and its Stereochemical Findings. (6).[1] A Synthesis of *dl-threo*-2-Benzamido-1-*p*-nitrophenyl-1,3-propanediol from *trans*-*p*-Nitrocinnamyl Alcohol.

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In our recent investigations,[1,2] a new synthetic method for *dl*-phenylserinols from *trans*-cinnamyl alcohol has been established. Since this method is expected to be successfully applicable to the synthesis of chloramphenicol, derivation of *dl*-*p*-nitrophenylserinols from *trans*-*p*-nitrocinnamyl alcohol (I) was attempted and examined from stereochemical view in connection with the previous findings.

trans-*p*-Nitrocinnamyl alcohol (I), m.p. 127°,[3] was treated with bromine in carbon tetrachloride to give *dl*-2,3-dibromo-3-*p*-nitrophenylpropanol (II), m.p. 87~89°, which afforded the O-benzoate (III) on treatment with benzoyl chloride in pyridine. The configuration of the dibromo compound (II) was assigned as *erythro* on the ground of being identical

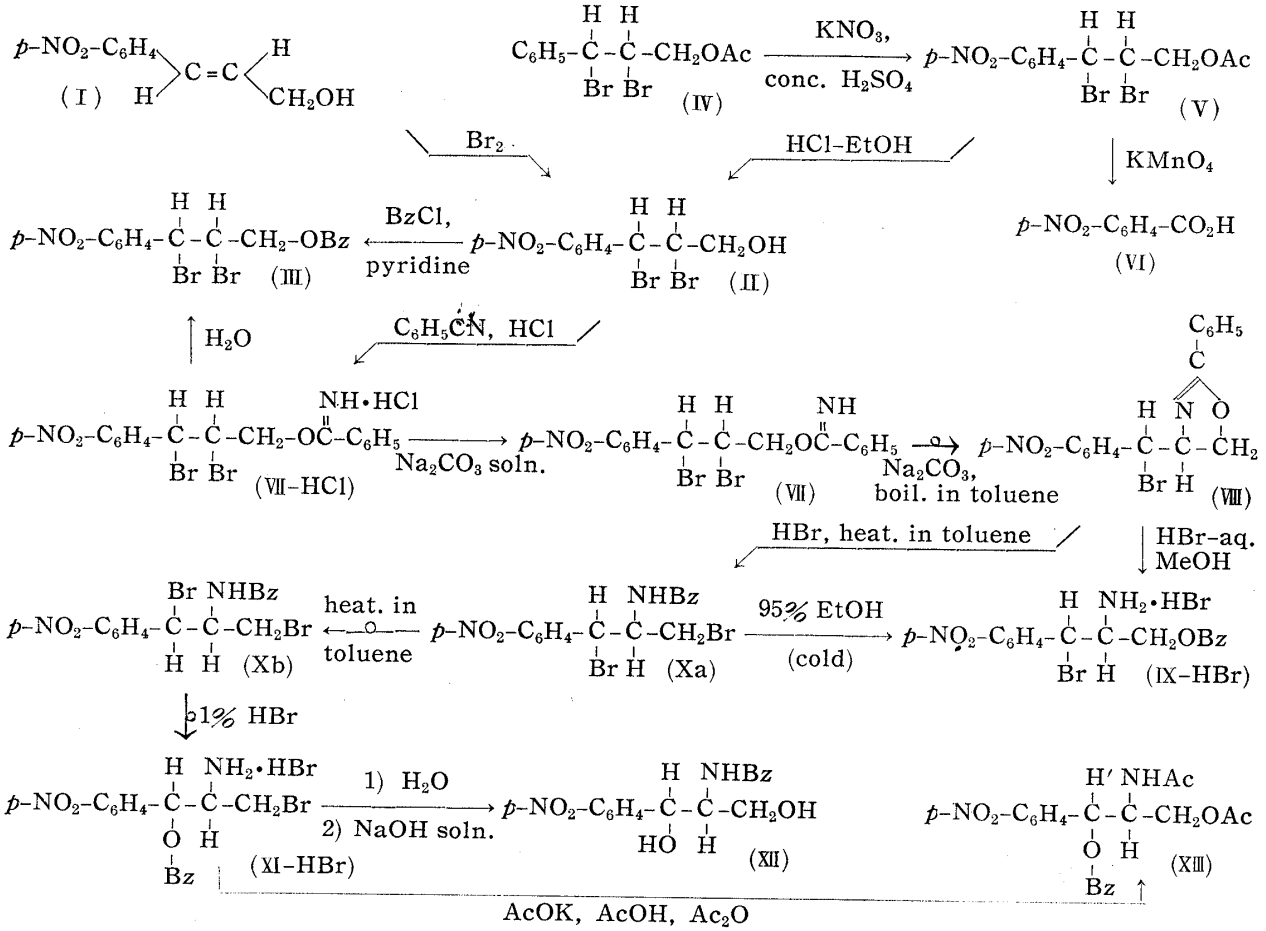


Chart 1.

* This constitutes part of a series entitled "Studies in Stereochemistry" by T. Taguchi.
** Katakasu, Fukuoka (友枝宗光).
1) Part 5 : This Bulletin, **5**, 189(1957).
2) Part 1 : J. Am. Chem. Soc., **78**, 1468(1955).
3) H. Meerwein *et al.* : J. prakt. Chem., [2], **147**, 211(1936).

with *dl-erythro*-2,3-dibromo-3-*p*-nitrophenylpropanol derived from *dl-erythro*-2,3-dibromo-3-phenylpropyl acetate (IV)[4] by nitration with KNO_3 and conc. H_2SO_4 followed by saponification. Additionally the *para*-occupation of the nitro radical on benzene ring of (II) was also proved by derivation of the acetate (V) into *p*-nitrobenzoic acid (VI) by oxidation with potassium permanganate.

A dry ether solution of (II) and benzonitrile was saturated with HCl and kept in the cold for several days to give *dl-erythro*-2,3-dibromo-3-*p*-nitrophenylpropyl benzimidate (VII) hydrochloride, which was converted into the free base (VII) by treatment with Na_2CO_3 solution. Boiling (VII-HCl) in water gave (III), which provides an evidence for the imidate structure. The imidate (VII) was boiled in toluene with anhyd. Na_2CO_3 to give *dl-threo*-4-*p*-nitrophenylbromomethyl-2-phenyl-Δ^2-oxazoline (VIII), the oxazoline structure of which was proved by the infrared spectrum and by the fact that (VIII) easily added one mole of water on treatment with HBr-hydrous MeOH to convert into *dl-threo*-2-amino-3-bromo-3-*p*-nitrophenylpropyl benzoate (IX) hydrobromide. The fact that the displacement of Br atom by =NH radical did not take place at C-3 but at C-2, is well conceivable by constructing a Stuart-type model of the imidate (VII), in which =NH radical is spatially arranged to be favorable for displacement rather at C-2 than at C-3, as shown in Fig. 1 (a and a'). Then, the *threo*-assignment of (VIII) was supported by the recognized fact that a similar ring-closure reactions[1,2] proceed through the internal S_N2 mechanism with inversion and the same assignment to (IX-HBr) was made because the formation reaction does not involve the breaking of any bonds to asymmetric carbon atoms.

On boiling the oxazoline (VIII) hydrobromide in toluene for 1 hour, *dl-threo*-1,3-dibromo-1-*p*-nitrophenyl-2-propyl benzamide (Xa) was obtained as a consequence of ring opening by addition of HBr without any configurational change at asymmetric carbon atoms. The infrared spectrum of (Xa) revealed a definite acylamide structure.

(Xa) was kept in hydrous EtOH at room temperature for more than one week to give (IX-HBr), but, when (Xa) was boiled in toluene with or without dry HBr for several hours, it changed into an oily product which was then partially hydrolyzed in aq. HBr to give a solid of empirical formula $C_{16}H_{15}O_4N_2Br \cdot HBr$. The same oil was also obtained from the imidate (VII) or the hydrobromide of the oxazoline (VIII) on heating in toluene for several hours. The configuration of the solid was proved to be *dl-threo*-2-amino-3-bromo-1-*p*-nitrophenylpropyl benzoate (XI) hydrobromide by the fact that its further hydrolysis in water caused the liberation of hydrobromic acid and a following treatment with NaOH solution gave a product which was identified as *dl-threo*-2-benzamido-1-*p*-nitrophenyl-1,3-propanediol (XII) by admixture. Further evidence for the structure of (XI-

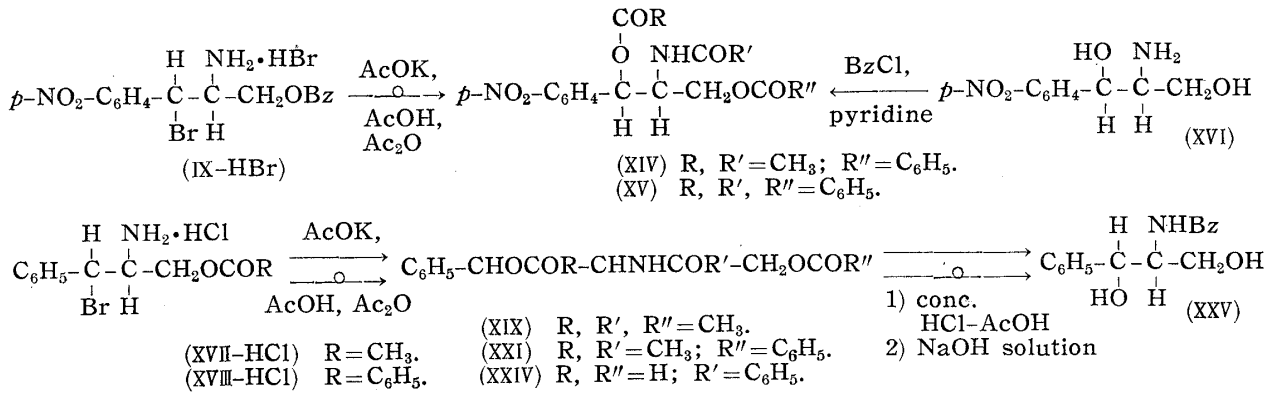
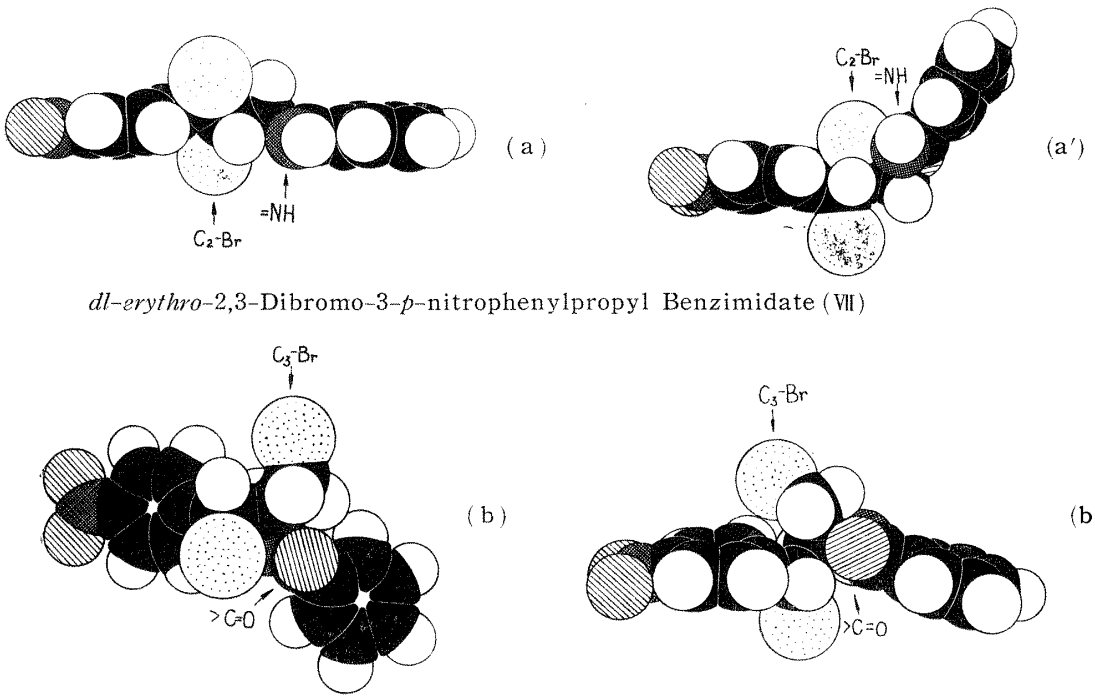


Chart 2.

4) It was derived from *dl-erythro*-2,3-dibromo-3-phenylpropanol[2] by treatment with Ac_2O; m.p. 86~88°.[5]

5) E. Grimaux: Bull. soc. chim. France, [2], **20**, 121.

Fig. 1 Stuart-type Atomic Models showing the Existence of Steric Hindrance



Comparative steric hindrance exists in (a′), (b′) and (c′), compared to (a), (b) and (c), respectively.

HBr) was provided by its derivation to *dl-threo*-2-acetamido-3-acetoxy-1-*p*-nitrophenylpropyl benzoate (XIII) on treatment with a mixture of potassium acetate, acetic acid, and acetic anhydride.

Thus the reaction course, (Xa) → oily product → (XI-HBr), is presumably explained by the thermal epimerization of (Xa) to the oily product, *dl-erythro*-1,3-dibromo-1-*p*-nitrophenyl-2-propyl benzamide (Xb), which then gave (XI-HBr) upon partial hydrolysis, showing the preference of the acyl participation to C-1. On the other hand, a similar partial hydrolysis of the *threo*-dibromide (Xa) gave, as mentioned above, (IX-HBr) by the acyl participation to C-3. It is well indicated by the construction of Stuart-type models (as shown in Fig. 1,b and b′, c and c′) of both dibromides (Xa and Xb) that favorable conformational arrangements of these compounds for acyl participation either to C-1 or to

C-3 reasonably explains the experimental results of partial hydrolysis.[6]

As a whole, each of the above-mentioned reactions was found to be in analogy with the corresponding one of similar courses starting from *dl-erythro*-2,3-dibromo-3-phenylpropanol and benzonitrile.[2] This means that the explanation for the whole process has been given with validity.

It was further considered of interest to estimate the probable stereospecificity in the displacement reaction of C-3-bromine of (IX-HBr) by OAc radical under dry conditions, in comparison with results of similar treatment of *dl-threo*-2-amino-3-bromo-3-phenylpropyl acetate (XVII) hydrochloride[1] and *dl-threo*-2-amino-3-bromo-3-phenylpropyl benzoate (XVIII) hydrochloride.[2] On boiling in a mixture of potassium acetate, acetic acid, and acetic anhydride, (IX-HBr) gave *dl*-2-acetamido-3-benzoyloxy-1-*p*-nitrophenylpropyl acetate (XIV) as a sole product. On saponification by boiling in 5% HCl and subsequent benzoylation with benzoyl chloride and pyridine, (XIV) gave a tribenzoate, which was proved to be identical with *dl-erythro*-2-benzamido-1-*p*-nitrophenyl-1,3-propanediol dibenzoate (XV), derived from *dl-erythro-p*-nitrophenylserinol (XVI),[7] by admixture. The triacyl compound (XIV) was also assigned *erythro* since such treatment of (XIV) to give (XV) does not involve the possibility of a configurational change. The result clearly indicates that the displacement reaction of C-3-bromine of (IX-HBr) by OAc radical under dry conditions did proceed through S_N2 mechanism with complete inversion.

On the other hand, a similar treatments of (XVII-HCl) and (XVIII-HCl), which have no NO_2 radical on the benzene ring, with a mixture of potassium acetate, acetic acid, and acetic anhydride, gave triacyl compounds, (XIX) and (XXI), respectively, as major products. The configuration of both products was deduced as an epimeric mixture of *dl*-2-acetamido-1-phenyl-1,3-propanediol diacetate and of *dl*-2-acetamido-3-benzoyloxy-1-phenylpropyl acetate, respectively, since they were equally converted into an epimeric mixture of N-benzoyl-*dl*-phenylserinols (XXIV) by successive saponification and benzoylation, and was finally converted into the pure *threo* epimer (XXV) after N→O and reverse acyl migration reactions.[1] It is then well deduced that the displacement of C-3-bromine of (XVII-HCl) and (XVIII-HCl) by OAc radical under dry condition was accompanied by both inversion and retention of configuration.

Thus there seemed to be a remarkable difference in steric results between the acetolysis of (IX-HBr) holding NO_2 radical on benzene ring and (XVII-HCl) or (XVIII-HCl) without such NO_2 radical. The result in the case of (XVII-HCl) or (XVIII-HCl) showed apparently the contribution of S_N1 mechanism, but in the case of (IX-HBr), as the effect of NO_2 substituent on benzene ring has well been discussed,[8] the development of positive charge on C-3 of (IX-HBr) by the electron-attracting character of NO_2 radical seemed to prevent the departure of Br^- from C-3 and set the reaction in S_N2. In other words, it is presumed that the rate-retarding effect of NO_2 radical to S_N1 overcomes some effects which favor S_N1.

An oil (XX) was obtained as a by-product during the course of (XVII-HCl) → (XIX) and also a solid (XXII) and a similar oil (XXIII) during the course of (XVIII-HCl) → (XXI). Though their configurations could not be proved, acid hydrolysis of the solid (XXII) and the oils (XX or XXIII), followed by benzoylation, gave an epimeric mixture of N-benzoyl-*dl*-phenylserinol (XXIV) and pure *threo* epimer (XXV), respectively, whose reaction mechanisms are still not clear.

I wish to express my thanks to Prof. Taguchi for his kind advice and encouragement through the course of this work, and to Mr. Koga and Mr. Sakimura for their cooperations in a part of

6) Similar result was obtained by J. Farkas: Chem. Listy, **47**, 552 (1953).
7) L.M. Long, H.D. Troutman: J. Am. Chem. Soc., **71**, 2473 (1949).
8) A. Streitweiser, Jr.: Chem. Revs., **1956**, 589, 600, 612.

this work. My 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, and to the Sankyo Co. for supplying *threo* and *erythro* epimers of *dl*-*p*-nitrophenylserinol and for the infrared spectral determination. The expenses of this investigation have been partly defrayed by a Grant in Aid for Scientific Research from the Ministry of Education.

Experimental

***trans*-*p*-Nitrocinnamyl Alcohol (I)**—Derived from *trans*-*p*-nitrocinnamyl aldehyde by Meerwein-Ponndorf reduction.[3] It melted at 127°.

***dl-erythro*-2,3-Dibromo-3-*p*-nitrophenylpropanol (II)**—i) From (I): To a solution of 10 g. of (I) in 70 cc. of CCl_4, a solution of 10 g. of Br_2 in 20 cc. of CCl_4 was added dropwise at room temperature and the reaction mixture set aside for 30 mins.; the whole treatment was carried out with stirring. The solution was washed with sat. $NaHSO_3$, sat. $NaHCO_3$, and H_2O, and dried over anhyd. Na_2SO_4. After filtration, the solution was concentrated *in vacuo* to afford a solid, m.p. 86~89°; yield, 12.7 g. Recrystallization from CCl_4 gave colorless needles, m.p. 87~89°. *Anal.* Calcd. for $C_9H_{10}O_3NBr_2$ (II): C, 31.76; H, 2.96; N, 4.12. Found: C, 31.94; H, 2.85; N, 4.01.

ii) From *dl-erythro*-2,3-Dibromo-3-*p*-nitrophenylpropyl Acetate (V): A solution of 1 g. of (V) in a mixture of 10 cc. of 20% HCl and 40 cc. of 50% EtOH was boiled for 2.5 hrs. and concentrated *in vacuo* to afford a solid. Recrystallization from petr. benzine gave colorless needles, m.p. 86~89°, alone and on admixture with a sample of (II) obtained by procedure (i); yield, 280 mg.

***dl-erythro*-2,3-Dibromo-3-*p*-nitrophenylpropyl benzoate (III)**—i) From (II): To a solution of 300 mg. of (II) in 2 cc. of pyridine, a solution of 300 mg. of BzCl in 1 cc. of pyridine was added at 0°, the solution was kept in the cold for 3 hrs., and poured into ice-water to deposit a pale yellow solid in a good yield. Recrystallization from EtOH gave pale yellow prisms, m.p. 119~121°. *Anal.* Calcd. for $C_{16}H_{14}O_4NBr_2$ (III): C, 43.27; H, 3.18; N, 3.15. Found: C, 43.32; H, 3.34; N, 3.36.

ii) From *dl-erythro*-2,3-Dibromo-3-*p*-nitrophenylpropyl Benzimidate (VII) Hydrochloride: A suspension of 100 mg. of (VII-HCl) in 5 cc. of H_2O was boiled for 1 hr. and after cooling, the separated oil crystallized. Recrystallization from EtOH gave pale yellow prisms, m.p. 119~120°, alone and on admixture with a sample of (III) obtained by procedure (i); yield, 30 mg.

***dl-erythro*-2,3-Dibromo-3-*p*-nitrophenylpropyl Acetate (V)**—Ten grams of *dl-erythro*-2,3-dibromo-3-phenylpropyl acetate (IV)[4] was added in small portions to a solution of 4.5 g. of KNO_3 in 112.5 g. of conc. H_2SO_4 at −5° during 1 hr., and the solution kept below 0° for further 1 hr.; the whole treatment being carried out with vigorous stirring. The solution was poured into ice water, avoiding a rise of temperature, the deposited solid was filtered, washed with H_2O, and dried; m.p. 103~120°; wt., 7.5 g. Recrystallization from CCl_4 gave colorless prisms, m.p. 130~132°; yield, 3.5 g. *Anal.* Calcd. for $C_{11}H_{11}O_4NBr_2$ (V): C, 34.67; H, 2.94; N, 3.68. Found: C, 35.17; H, 2.69; N, 3.72.

Oxidation of (V) to *p*-Nitrobenzoic Acid (VI)—To a hot suspension of 1 g. of (V) in 50 cc. of 1% NaOH, ca. 4 g. of $KMnO_4$ was added in small portions with stirring until the violet color persisted. The solution was decolorized by addition of a small volume of EtOH, and after filtration, the solution was concentrated *in vacuo* to a small volume and acidified with aq. H_2SO_4 to deposit a solid. Recrystallization from benzene gave pale yellow needles, m.p. 234~236°, alone and on admixture with a sample of *p*-nitrobenzoic acid. *Anal.* Calcd. for $C_7H_5O_4N$(VI): N, 8.38. Found: N, 8.34.

***dl-erythro*-2,3-Dibromo-3-*p*-nitrophenylpropyl Benzimidate (VII) Hydrochloride**—A solution of 11 g. of (II) and 3.3 g. of benzonitrile in 10 cc. of dry ether was saturated with dry HCl at 0°. Colorless needles, precipitated after standing in the cold for several days, were collected, washed with dry ether, and dried over NaOH *in vacuo*, m.p. 142~144°; yield, 8.1 g. *Anal.* Calcd. for $C_{16}H_{15}O_3N_2Br_2Cl$ (VII-HCl): N, 5.85. Found: N, 5.78.

***dl-erythro*-2,3-Dibromo-3-*p*-nitrophenylpropyl Benzimidate (VII)**—Seven grams of (VII-HCl) was ground with 20 cc. of cold 5% Na_2CO_3 in a mortar for 10 mins. and the solid was filtered, washed with H_2O, and dried; m.p. 117~128°; yield, 6.3 g. Recrystallization from acetone gave pale yellow needles. m.p. 128~129°. *Anal.* Calcd. for $C_{16}H_{14}O_3N_2Br_2$ (VII): C, 43.46; H, 3.19; N, 6.34. Found: C, 43.42; H, 2.85; N, 6.30.

***dl-threo*-4-*p*-Nitrophenylbromomethyl-2-phenyl-Δ^2-oxazoline (VIII)**—A mixture of 500 mg. of (VII) and 1.0 g. of anhyd. Na_2CO_3 in 10 cc. of toluene was boiled with occasional shaking for 1 hr. After filtration while hot, yellow crystals deposited, which were collected and recrystallized from benzene to pale yellow prisms, m.p. 166~168°; yield, 180 mg. *Anal.* Calcd. for $C_{16}H_{13}O_3N_2Br$ (VIII): C, 53.20; H, 3.63; N, 7.76. Found: C, 53.09; H, 3.98; N, 7.82. I.R. λ_{max}^{Nujol} μ: 6.05 (>C=N—); 6.58, 7.44 (*p*-NO_2-); 6.24, 6.32, 6.68 (-C_6H_5).

***dl-threo*-2-Amino-3-bromo-3-*p*-nitrophenylpropyl Benzoate (IX) Hydrobromide**—A solution of 900 mg. of (VIII) in a mixture of 0.8 cc. of 31% HBr and 180 cc. of MeOH was boiled for 5 mins. and kept at room temperature for 2 days. After concentration *in vacuo*, the solid obtained was recrystallized from MeOH-ether to colorless needles, m.p. 186~188°(decomp.); yield, 1.0 g. *Anal.* Calcd.

for $C_{16}H_{16}O_4N_2Br_2$(IX-HBr): C, 41.76; H, 3.51; N, 5.90. Found: C, 42.20; H, 3.60; N, 6.19.

***dl-threo*-1,3-Dibromo-1-*p*-nitrophenyl-2-propyl Benzamide (Xa)**—A solution of 500 mg. of (VIII) in 60 cc. of dry benzene was saturated with dry HBr and concentrated *in vacuo* to leave an oily product. The product was mixed with 40 cc. of dry toluene, the mixture was boiled for 1 hr., and concentrated *in vacuo* to leave a solid, m.p. 138~141°; yield, 480 mg. Recrystallization from benzene-petr. benzine gave colorless prisms, m.p. 144~145°. *Anal.* Calcd. for $C_{16}H_{14}O_3N_2Br_2$ (Xa): C, 43.46; H, 3.19; N, 6.34. Found: C, 43.76; H, 3.56; N, 6.29. I.R. $\lambda_{max}^{Nujol}\mu$: 2.99, 6.07, 6.55 ($-NHCOC_6H_5$); 6.57, 7.42 (p-NO_2-); 6.22, 6.32, 6.70 ($-C_6H_5$).

Partial Hydrolysis of *dl-threo*-1,3-Dibromo-1-*p*-nitrophenyl-2-propyl Benzamide (Xa) in Cold 95% EtOH to (IX-HBr)—The solution of 200 mg. of (Xa) dissolved in 40 cc. of 95% EtOH was kept at room temperature for 2 weeks. The solution was concentrated *in vacuo* to leave a solid, m.p. 183~189°(decomp.); yield, 185 mg. Recrystallization from MeOH-ether gave colorless needles, m.p. 186~189°(decomp.), alone and on admixture with a sample of (IX-HBr) derived from (VIII). *Anal.* Calcd. for $C_{16}H_{16}O_4N_2Br_2$ (IX-HBr): N, 5.90. Found: N, 6.06.

***dl-threo*-2-Amino-3-bromo-1-*p*-nitrophenylpropyl Benzoate (XI) Hydrobromide**—i) From (VII) via the assumed *dl-erythro*-1,3-Dibromo-1-*p*-nitrophenyl-2-propyl Benzamide (Xb): A solution of 500 mg. of (VII) in 5 cc. of toluene was boiled for 6 hrs. At the beginning, colorless needles appeared and dissolved soon afterward. The solution was concentrated *in vacuo* to leave an oily product (Xb). This was heated in 1 cc. of 1% HBr on a steam bath for 1 hr. with occasional shaking and crystals deposited gradually while heating. The crystals were collected and washed with a mixture of acetone and ether, m.p. 205~206°(decomp.); yield, 170 mg. Recrystallization from EtOH gave colorless needles, m.p. 206~207°(decomp.), alone and on admixture with a sample of (XI-HBr) derived from (Xa). *Anal.* Calcd. for $C_{16}H_{16}O_4N_2Br_2$ (XI-HBr): C, 41.76; H, 3.51; N, 5.90. Found: C, 41.95; H, 3.30; N, 6.09.

ii) From (VIII) via (Xb): A solution of 200 mg. of (VIII) in 10 cc. of dry toluene was saturated with dry HBr and boiled for 7 hrs., and concentrated *in vacuo* to leave an oily product (Xb). This was heated in 1 cc. of 1% HBr for 1 hr. with occasional shaking and crystals deposited. After filtration, recrystallization from MeOH gave colorless needles, m.p. 204~206°(decomp.), alone and on admixture with a sample of (XI-HBr) derived from (Xa); yield, 150 mg. *Anal.* Calcd. for $C_{16}H_{16}O_4N_2Br_2$ (XI-HBr): N, 5.90. Found: N, 5.77.

iii) From (Xa) via (Xb): a) Without dry HBr: A solution of 200 mg. of (Xa) in 4 cc. of dry toluene was boiled for 14 hrs. and concentrated *in vacuo* to leave an oily product (Xb). The oil was heated in 0.8 cc. of 1% HBr on a steam bath for 1 hr. to afford crystals. Recrystallization from MeOH-ether gave colorless needles, m.p. 205~207°(decomp.); yield, 110 mg. *Anal.* Calcd. for $C_{16}H_{16}O_4N_2Br_2$ (XI-HBr): C, 41.76; H, 3.51; N, 5.90. Found: C, 41.83; H, 3.48; N, 6.25.

b) With dry HBr: A solution of 1.0 g. of (Xa) in 10 cc. of dry toluene was saturated with dry HBr, boiled for 7 hrs., and concentrated *in vacuo* to leave an oily product (Xb). This was heated in 2 cc. of 1% HBr on a steam bath for 1 hr. to afford (XI-HBr) as colorless needles, m.p. 205~207°(decomp.), alone and on admixture with a sample derived from (Xa) without dry HBr; yield, 700 mg. *Anal.* Calcd. for $C_{16}H_{16}O_4N_2Br_2$ (XI-HBr): N, 5.90. Found: N, 6.43.

***dl-threo*-2-Benzamido-1-*p*-nitrophenyl-1,3-propanediol (XII)**—A solution of 120 mg. of (XI-HBr) in 12 cc. of H_2O was boiled for 3 hrs.; the pH of the solution changed from 5.4 to 2.4. The solution was concentrated *in vacuo* to a small volume and made alkaline with 10% NaOH to leave an oily product which then crystallized. Recrystallization from AcOEt gave colorless needles, 160~162°, alone and on admixture with an authentic sample of *dl-threo*-2-benzamido-1-*p*-nitrophenyl-1,3-propanediol[7]; yield, 70 mg. *Anal.* Calcd. for $C_{16}H_{16}O_5N_2$ (XII): C, 60.75; H, 5.10; N, 8.86. Found: C, 60.99; H, 4.72; N, 8.64.

***dl-threo*-2-Acetamido-3-acetoxy-1-*p*-nitrophenylpropyl Benzoate (XIII)**—A solution of 350 mg. of (XI-HBr) in a mixture of 200 mg. of anhyd. AcOK, 8 cc. of AcOH, and 2 cc. of Ac_2O was boiled for 2 hrs., and concentrated *in vacuo*. The AcOEt extract of the residue was washed with H_2O, dried over anhyd. Na_2SO_4, and concentrated *in vacuo*. After addition of a small volume of benzene, crystals that deposited were collected, m.p. 149~153°; yield, 280 mg. Recrystallization from 50% EtOH gave colorless prisms, m.p. 152~154°. *Anal.* Calcd. for $C_{20}H_{20}O_6N_2$ (XIII): C, 60.00; H, 5.03; N, 7.00. Found: C, 60.53; H, 5.43; N, 7.26.

Treatment of (IX-HBr) with AcOK·AcOH·Ac_2O to form *dl-erythro*-2-Acetamido-3-benzoyloxy-1-*p*-nitrophenylpropyl Acetate (XIV)—A solution of 3.315 g. of (IX-HBr) in a mixture of 1.60 g. of anhyd. AcOK, 48 cc. of AcOH, and 12 cc. of Ac_2O was boiled for 2 hrs. and poured into ice water to deposit an oily product. The AcOEt extract of the product was washed with satd. $NaHCO_3$ and H_2O, and dried over anhyd. Na_2SO_4. After filtration, the solution was concentrated *in vacuo* to afford a solid, m.p. 133~140°; wt., 2.36 g. Recrystallization from benzene gave colorless needles, m.p. 142~144°; yield, 1.85 g. *Anal.* Calcd. for $C_{20}H_{20}O_6N_2$ (XIV): C, 60.00; H, 5.03; N, 7.00. Found: C, 59.54; H, 5.70; N, 7.23.

***dl-erythro*-2-Benzamido-1-*p*-nitrophenyl-1,3-propanediol Dibenzoate (XV)**—i) From *dl-erythro*-

2-Amino-1-*p*-nitrophenyl-1,3-propanediol (XVI)[7]: A mixture of 120 mg. of (XVI) added to a cold mixture of 400 mg. of BzCl and 3 cc. of pyridine was kept over night at room temperature and poured into ice water to give an oily product. The AcOEt extract of the product was washed with 5% HCl, satd. $NaHCO_3$, and H_2O, and dried over anhyd. Na_2SO_4. After concentration of the filtrate, a solid deposited and was recrystallized from MeOH-acetone to colorless needles, m.p. 199~200.5°; yield, 200 mg. *Anal.* Calcd. for $C_{30}H_{24}O_7N_2$ (XV): C, 68.69; H, 4.61; N, 5.34. Found: C, 68.27; H, 4.85; N, 5.37.

ii) From (XIV): A suspension of 1.52 g. of (XIV) in 300 cc. of 5% HCl was boiled for 5 hrs., all the crystals of (XIV) dissolved within 2 hrs. The solution was concentrated *in vacuo* and dried over NaOH to leave an oily product. The product was mixed with 2.28 g. of BzCl in 15 cc. of pyridine at 0°, kept at room temperature over night, and poured into ice water to deposit a solid, m.p. 184~192°; wt., 2.07 g. Recrystallization from MeOH-acetone gave colorless needles, m.p. 199~201°, alone and on admixture with a sample of (XV) derived from (XVI). *Anal.* Calcd. for $C_{30}H_{24}O_7N_2$ (XV): N, 5.34. Found: N, 5.31.

Treatment of *dl-threo*-2-Amino-3-bromo-3-phenylpropyl Acetate (XVII) Hydrochloride[1] with AcOK·AcOH·Ac_2O to form a Mixture of *dl-threo*- and *-erythro*-2-Acetamido-1-phenyl-1,3-propanediol Diacetate (XIX)—A solution of 1.0 g. of (XVII-HCl) in a mixture of 1.0 g. of anhyd. AcOK, 22.5 cc. of AcOH, and 7.5 cc. of Ac_2O was boiled for 10 hrs. After filtration of deposited KBr, the solution was concentrated *in vacuo* to leave a solid residue. The soild was extracted with AcOEt, washed with satd. $NaHCO_3$ and H_2O, and dried over anhyd. Na_2SO_4. After filtration, the solution was concentrated *in vacuo* to leave crystals, m.p. 114~116°. Recrytallization from AcOEt gave colorless needles, m.p. 115~116°; yield, 320 mg. *Anal.* Calcd. for $C_{15}H_{19}O_5N$ (XIX): C, 61.41; H, 6.54; N, 4.78. Found: C, 61.67; H, 6.86; N, 4.98.

Concentration of the AcOEt mother liquor gave an oil (XX); wt., 140 mg.

Treatment of *dl-threo*-2-Amino-3-bromo-3-phenylpropyl Benzoate (XVIII) Hydrochloride with AcOK·AcOH·Ac_2O to form a Mixture of *dl-threo*- and *-erythro*-2-Acetamido-3-benzoyloxy-1-phenylpropyl Acetate (XXI)—A solution of 5.0 g. of (XVIII-HCl) in a mixture of 2.5 g. of anhyd. AcOK, 80 cc. of AcOH, and 20 cc. of Ac_2O was boiled for 2.5 hrs. After cooling, deposited KBr was filtered off and the solution was concentrated *in vacuo* to a small volume, and poured into ice water to deposit an oily product, which was then extracted with AcOEt. The AcOEt layer was washed with satd. $NaHCO_3$ and H_2O, and dried over anhyd. Na_2SO_4. After filtration, the solution was concentrated, followed by addition of a small volume of ether to deposit crystals, m.p. 109~113°; wt., 2.38 g. Recrystallization from benzene-petr. benzine gave colorless prisms, m.p. 115~117°; yield, 2.12 g. *Anal.* Calcd. for $C_{20}H_{21}O_5N$ (XXI): C, 67.59; H, 5.96; N, 3.94. Found: C, 67.79; H, 6.04; N, 3.70.

Concentration of the ethereal mother liquor gave colorless needles (XXII). After recrystallization from benzene it melted at 126~129°, and depressed the m.p. of (XXI) on admixture; yield, 240 mg. *Anal.* Found: C, 65.79; H, 5.80; N, 4.28.

Further concentration of the ethereal mother liquor gave an oil (XXIII); wt., 1.90 g.

***dl-threo*-2-Benzamido-1-phenyl-1,3-propanediol (XXV)**—i) From (XIX) via a Mixture of *dl-threo*- and *-erythro*-2-Benzamido-1-phenyl-1,3-propanediol (XXIV): A solution of 200 mg. of (XIX) in 5 cc. of 90% EtOH containing 4% KOH was boiled for 1 hr. After cool, the solution was made neutral with addition of dil. HCl, concentrated *in vacuo* to a small volume, and benzoylated with 150 mg. of BzCl in 1.5 cc. of benzene and 10% NaOH by the Schotten-Baumann method to afford crystals. The crystals were dissolved in 20 cc. of hydr. MeOH containing 21.4 mg. of NaOH, the solution was boiled for 1 hr., and concentrated *in vacuo* to leave a solid residue. The solid was extracted with AcOEt, washed with satd. $NaHCO_3$ and H_2O, and dried over anhyd. Na_2SO_4. After filtration, the solution was concentrated *in vacuo* to afford crystals, m.p. 125°; yield, 80 mg. Recrystallization from AcOEt gave colorless needles, m.p. 131~132°. *Anal.* Calcd. for $C_{16}H_{17}O_3N$ (XXIV): C, 70.83; H, 6.32; N, 5.16. Found: C, 71.02; H, 6.31; N, 4.98.

The saponification of (XIX) in 5% HCl gave a similar result. A solution of 300 mg. of (XIX) in 5 cc. of 5% HCl was boiled for 2.5 hrs., concentrated, and benzoylated by the Schotten-Baumann method to give colorless needles (XXIV), m.p. 130~131°; yield, 150 mg.

A solution of 90 mg. of (XXIV) in a mixture of 0.4 cc. of conc. HCl and 0.8 cc. of AcOH was boiled for 5 mins. and concentrated *in vacuo* to give an oily residue, which was dissolved in a small volume of H_2O and made alkaline with 10% NaOH to give an oily product, which then crystallized. Recrystallization from AcOEt gave colorless needles, m.p. 163~164°, alone and on admixture with an authentic sample of *dl-threo*-2-benzamido-1-phenyl-1,3-propanediol[1]; yield, 60 mg. *Anal.* Calcd. for $C_{16}H_{17}O_3N$ (XXV): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.63. H, 6.27; N, 5.17.

ii) From the Oil (XX) obtained in the Course of (XVII-HCl) to (XIX): A suspension of 120 mg. of (XX) in 40 cc. of 5% HCl was boiled for 5.5 hrs., concentrated *in vacuo*, and dried over NaOH to leave an oily product. The oil was benzoylated with 300 mg. of BzCl in 3 cc. of pyridine to give a crude tribenzoate, m.p. 173~190°; wt., 135 mg. The tribenzoate was dissolved in a mixture of 30 mg. of NaOH in 40 cc. of 95% EtOH and the solution kept over night at room temperature. The solution was concentrated *in vacuo* to leave a solid residue, which was extracted with AcOEt and after con-

centration of the AcOEt extract crystals deposited. Recrystallization from AcOEt gave colorless needles, m.p. 163~165°, alone and on admixture with an authentic sample of (XXV); yield, 50 mg.

iii) From (XXI) via (XXIV) : A solution of 1.50 g. of (XXI) in 300 cc. of 5% HCl was boiled for 5 hrs., concentrated *in vacuo*, and dried over NaOH to leave an oily product. The benzoylation of the product with 3.0 g. of BzCl in 15 cc. of pyridine gave a crude tribenzoate : wt., 2.60 g. The tribenzoate was then dissolved in a mixture of 520 mg. of NaOH in 250 cc. of 90% MeOH, the solution was boiled for 1 hr., and concentrated *in vacuo* to give an oily residue. The AcOEt extract of the residue was washed with H_2O, dried over anhyd. Na_2SO_4, and after filtration, the solution was concentrated to leave a solid, m.p. 115~128°; yield, 940 mg. Recrystallization from AcOEt gave colorless needles, m.p. 130~133°. *Anal.* Calcd. for $C_{16}H_{17}O_3N$ (XXIV) : C, 70.83; H, 6.32; N, 5,16. Found : C, 70.71; H, 6.53; N, 5.55.

Alternative use of NaOH for the saponification of (XXI), followed by similar treatments as in the former case, also gave (XXIV). A solution of 50 mg. of (XXIV) in a mixture of 0.15 cc. of conc. HCl and 0.3 cc. of AcOH was boiled for 5 mins., and concentrated *in vacuo* to give an oily residue, which was dissolved in a small volume of H_2O and made alkaline with 10% NaOH to give an oily product which then crystallized. Recrystallization from AcOEt gave colorless needles, m.p. 163~165°, alone and on admixture with an authentic sample of (XXV); yield, 35 mg.

iv) From the Solid (XXII) obtained in the Course of (XVIII-HCl) to (XXI), via (XXIV) : A solution of 140 mg. of (XXII) in 28 cc. of 5% HCl was boiled for 5 hrs., concentrated *in vacuo*, and dried over NaOH to leave an oily product. The benzoylation of the product with 280 mg. of BzCl in 3 cc. of pyridine gave a crude tribenzoate; wt., 220 mg. The solid was then dissolved in a mixture of 46 mg. of NaOH in 44 cc. of 90% MeOH, the solution was boiled for 20 mins., concentrated *in vacuo* to a small volume, and after addition of H_2O, extracted with AcOEt. The AcOEt layer was dried over anhyd. Na_2SO_4, and after filtration, the solution was concentrated to a small volume. After addition of ether a solid deposited, m.p. 119~129°; wt., 80 mg. Recrystallization from AcOEt gave colorless needles (XXIV), m.p. 128~133°; yield, 55 mg. *Anal.* Calcd. for $C_{16}H_{17}O_3N$: N, 5.16. Found: N, 4.84.

Similarly, 30 mg. of (XXIV) was treated with a mixture of 0.1 cc. of conc. HCl and 0.2 cc. of AcOH, followed by treatment with 10% NaOH to give a solid. Recrystallization from AcOEt gave colorless needles, m.p. 163~165°, alone and on admixture with an authentic sample of (XXV); yield, 20 mg.

v) From the oil (XXIII) obtained in the Course of (XVIII-HCl) to (XXI) : A suspension of 1.0 g. of (XXIII) in 100 cc. of 5% HCl was boiled for 5 hrs.; the oil then went into solution. The solution was concentrated *in vacuo* and dried over NaOH to leave an oily product. Benzoylation of the product with 2.0 g. of BzCl in 10 cc. of pyridine gave a crude tribenzoate; wt., 1.17 g. A solution of 1.020 g. of the tribenzoate dissolved in a mixture of 210 mg. of NaOH in 100 cc. of 90% MeOH was boiled for 1 hr. and concentrated *in vacuo* to give a solid, m.p. 145~159°; wt., 330 mg. Recrystallization from AcOEt gave colorless needles, m.p. 163~165°, alone and on admixture with an authentic sample of (XXV); yield, 270 mg.

Summary

A new synthesis of *dl-threo*-2-benzamido-1-*p*-nitrophenyl-1,3-propanediol from *trans*-*p*-nitrocinnamyl alcohol was described and the reaction mechanisms involved in the synthesis were discussed in connection with earlier conclusions. Stereospecificity in the displacement of C-3-bromine of *dl-threo*-2-amino-3-bromo-3-*p*-nitrophenylpropyl benzoate system in a dry condition was examined, hereby special effect of NO_2 radical on benzene ring to the displacement was presumed.

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