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dl-Phenylserinols: A New Synthesis and its Stereochemical Findings. I¹

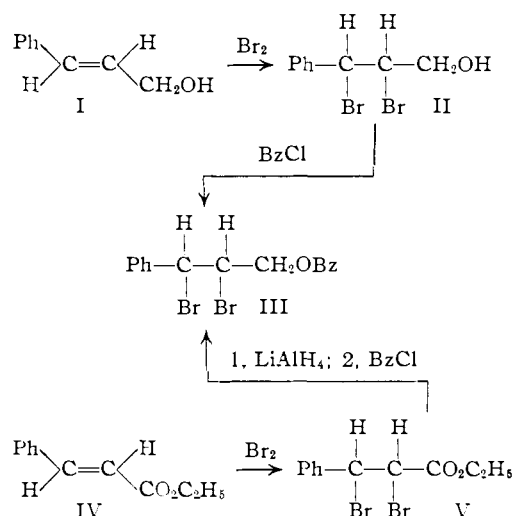
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RECEIVED AUGUST 2, 1955

A new synthesis of *dl*-*threo*-phenylserinol from *trans*-cinnamic alcohol is described. Configurations are assigned to the intermediate products formed in the synthesis and evidence is presented for the epimerization of *dl*-*threo*-1-phenyl-2-benzoylamino-1,3-dibromopropane by heat to the *erythro* form.

It is interesting from the standpoints of stereochemistry and of synthetic method that chloramphenicol may be obtained from cinnamic alcohol by stepwise addition and substitution reactions. Investigation of this problem has been begun with the synthesis of *dl*-phenylserinols.

The cinnamic alcohol (I), m.p. 30–33°, has been assigned the *trans* form.² On treatment with bromine in carbon tetrachloride this isomer gave *dl*-3-phenyl-2,3-dibromopropan-1-ol (II), m.p. 73–74°, in 84% yield, together with a small amount of an oil. Both the dibromide and the oil afforded the *O*-benzoate III, m.p. 114–115°, with benzoyl chloride. Assuming that compound (I) does have the *trans* configuration and that halogens, as is generally recognized, add preferentially to olefinic double bonds in a *trans* fashion the dibromide II may be assigned the *erythro* configuration. This assignment is confirmed by the fact that ethyl *trans*-cinnamate (IV) adds bromine to give ethyl *dl*-*erythro*-3-phenyl-2,3-dibromopropionate (V), whose configuration has been well established,³ and that reduction of V with lithium aluminum hydride resulted in *dl*-*erythro*-1-benzoyloxy-2,3-dibromo-3-phenylpropane (III), which was identical with that obtained from the cinnamic alcohol (I).



A dry ether solution of *dl*-*erythro*-3-phenyl-2,3-dibromopropan-1-ol (II) and benzonitrile upon saturation with hydrogen chloride and standing in the cold gave *dl*-*erythro*-3-phenyl-2,3-dibromopropyl benzimino ether (VI) hydrochloride, which was converted to the free base by treatment with sodium

carbonate. Boiling VI hydrochloride in water gave III; this provides evidence for the imino ether structure. Boiling VI dissolved in toluene gave a solid which then went into solution. The solid product was identified as VI hydrobromide, which might be formed by preferential combination of VI with hydrogen bromide liberated by replacement of the C₂-Br atom by the imino group. This result is analogous to that of Gabriel's in the case of β -bromoethyl benzimino ether.⁴

The toluene solution was evaporated to dryness under reduced pressure to leave an oily product (A) which was transformed to *dl*-*threo*-1-phenyl-1-benzoyloxy-2-amino-3-bromopropane (IX) hydrobromide by hydrolysis with 1% aqueous hydrobromic acid or aqueous ethanol. Conversion of IX hydrobromide to *dl*- ψ -*N*-benzoylnorephedrine (X)^{5,6} by catalytic reduction with palladium-charcoal, followed by treatment with aqueous sodium hydroxide, gave definite proof for the structure and configuration of IX. In the hydrolysis of the oily product A, leaflets of m.p. 123.5–125.5° were isolated in poor quantity; these were assumed to be *dl*-*erythro*-1-phenyl-1,2,3-tribromopropane (XI) on the basis of the empirical formula C₉H₉Br₃ and by analogy to the fact that dibromoethylene⁷ was obtained by pyrolysis of β -bromoethyl benzimino ether hydrobromide. A similar partial hydrolysis of VI-hydrobromide may have occurred here.

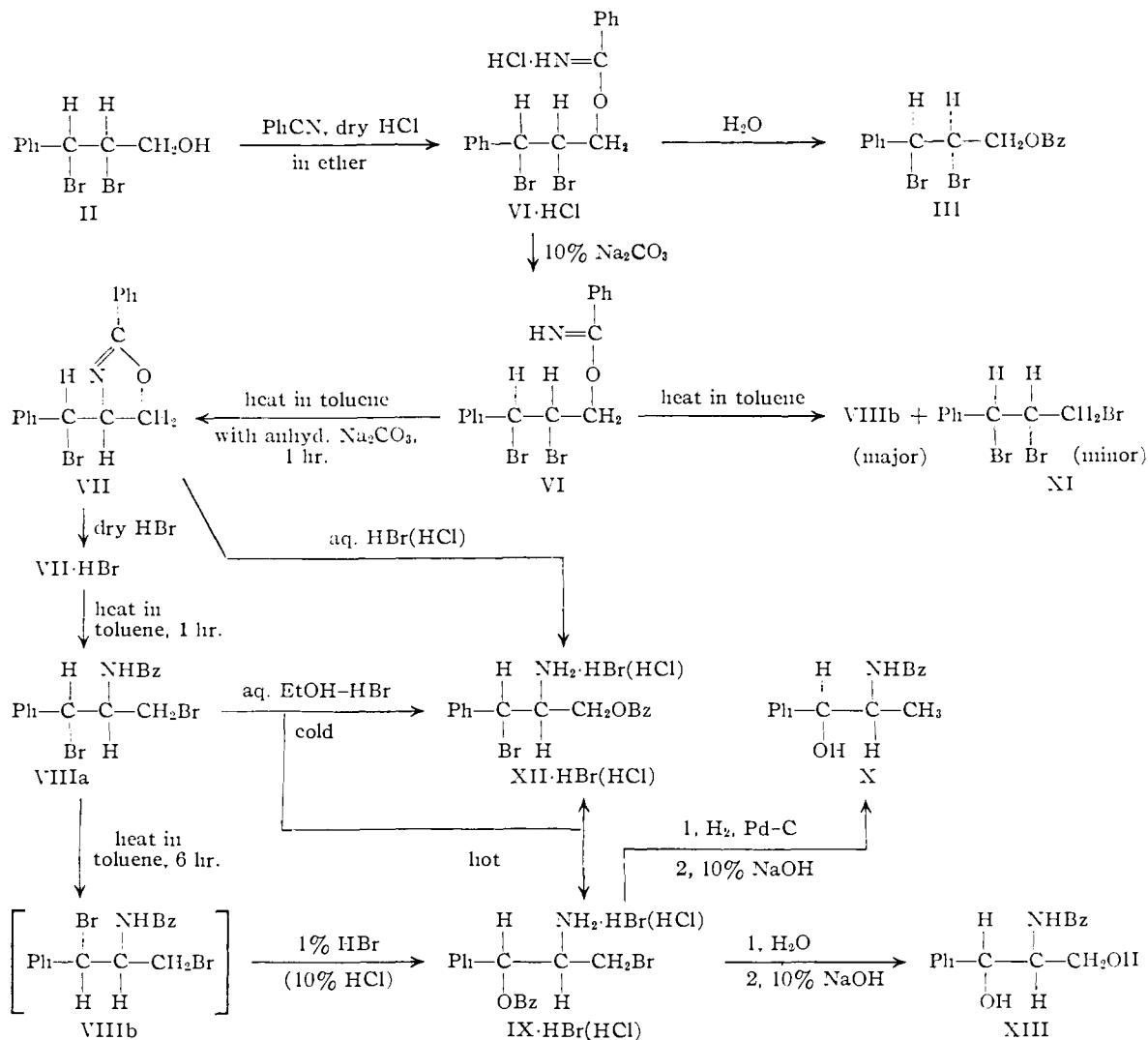
The pH of an aqueous solution of IX hydrobromide, upon boiling, rapidly decreased from 5.4 to 1.6, suggesting the liberation of hydrobromic acid by hydrolysis of the C₃-Br atom. The solution was concentrated under reduced pressure and made alkaline to yield an oily product, which slowly crystallized and was identical with *dl*-*threo*-1-phenyl-2-benzoylamino-1,3-propanediol (XIII) (73%). The oily product (A) was boiled in water for three hours and made alkaline to afford XIII directly in 21% yield.

By further analogy to Gabriel's results with β -bromoethyl benzimino ether it may be concluded that the oily product (A) consists mainly of *dl*-1-phenyl-2-benzoylamino-1,3-dibromopropane, formed from VI via *dl*-2-phenyl-4-phenylbromomethyl Δ^2 -oxazoline.

On the basis of the fact that substitution at the C₂-Br by the imino group may take place via S_N2 reaction with inversion, the oily product (A) may be assigned the *threo* form (VIIIa). However, A was found to give IX hydrobromide by presumably S_N2 acidic hydrolysis; this suggests the *erythro*

(1) Studies in Stereochemistry, VIII.
 (2) L. F. Hatch and H. E. Alexander, THIS JOURNAL, **72**, 5643 (1950).
 (3) E. Grovenstein, Jr., and D. E. Lee, *ibid.*, **75**, 2639 (1953).

(4) S. Gabriel and A. Neumann, *Ber.*, **25**, 2383 (1892).
 (5) W. N. Nagai and S. Kanao, *Ann.*, **470**, 157 (1920).
 (6) M. Honjo, *J. Pharm. Soc. Japan*, **73**, 368 (1953).
 (7) A. Pinner and F. Klein, *Ber.*, **10**, 1892 (1877).



form (VIIIb). To resolve these conflicting conclusions about the configuration of (A) further experiments were undertaken.

The imino ether VI was boiled in toluene with sodium carbonate for an hour to give *dl-threo*-2-phenyl-4-phenylbromomethyl- Δ^2 -oxazoline (VII). This compound (VII) added one mole of water on treatment with hydrochloric or hydrobromic acids to give the corresponding salts of *dl-threo*-1-benzoyloxy-2-amino-3-bromo-3-phenylpropane (XII).

The oxazoline VII hydrobromide was boiled in toluene for an hour to yield a neutral solid, m.p. 132–134°, accompanied by an oily product (B). The solid is characterized as *dl-threo*-1-phenyl-2-benzoylamino-1,3-dibromopropane (VIIIa) by microanalytical data, infrared spectra and the knowledge⁴ that oxazoline hydrohalide is converted to β -acylaminoethyl halide by heating. Both VIIIa and XII are assigned to be *threo* for the further reason that their formation reactions do not involve the breaking of any bonds to asymmetric carbon atoms. A further proof for the configuration of VIIIa is its hydrolysis in cold aqueous alcoholic hydrobromic acid to give XII hydrobromide. This result also indicates that acyl participation at C₃

is preferred over participation at C₁ in the *threo* isomer (VIIIa).

However, when VIIIa was boiled in toluene for several hours, it changed to an oily product (C) which was hydrolyzed in 1% warm aqueous hydrobromic acid to give IX hydrobromide. Also, the oily product (B) gave IX hydrobromide upon similar hydrolysis. Thus, the oily products (A, B and C) are commonly formed whenever VIIIa, as starting material or possible intermediate, is exposed to heat with exclusion of moisture, and give IX hydrobromide upon partial hydrolysis. Therefore, they are assumed to be identical and to be *dl-erythro*-1-phenyl-2-benzoylamino-1,3-dibromopropane (VIIIb). In each case the *erythro* isomer VIIIb was formed by epimerization of the *threo* form VIIIa.

Furthermore, a heated acidic hydrolysis of VIIIa, in contrast to that in the cold, gave IX and XII hydrobromides in the ratio of 1:4, IX hydrobromide presumably resulting from epimerization of VIIIa to VIIIb, followed by hydrolysis. Thus, there are no contradictions in the assignments of configuration to VIIIa and VIIIb, and in the epimerization of VIIIa to VIIIb.

Experimental⁸

dl-erythro-3-Phenyl-2,3-dibromopropan-1-ol (II).—To a solution of 100 g. of *dl-trans*-cinnamic alcohol in 1000 cc. of carbon tetrachloride, 131 g. of bromine in 100 cc. of carbon tetrachloride was added with stirring at -5° . The carbon tetrachloride solution was washed with dilute sodium bisulfite, saturated sodium bicarbonate and finally with water. The carbon tetrachloride solution was dried over anhydrous sodium sulfate and concentrated *in vacuo* till a solid appeared after chilling. Filtration and recrystallization from petroleum benzine gave large colorless needles, m.p. $73-74^{\circ}$,⁹ wt. 180 g. (84%). Concentration of the filtrate left an oily residue.

dl-erythro-1-Benzoyloxy-2,3-dibromo-3-phenylpropane (III). (a).—A mixture of 500 mg. of II and 500 mg. of benzoyl chloride was heated at $130-140^{\circ}$ for 1.5 hours. After cooling, the reaction mixture was mixed with saturated sodium bicarbonate and crystallized gradually in the cold. After filtration, recrystallization from methanol gave colorless needles, m.p. $114-115^{\circ}$, wt. 500 mg. (74%). *Anal.* Calcd. for $C_{16}H_{14}O_2Br_2$: C, 48.27; H, 3.54. Found: C, 48.33; H, 3.47. The oily residue described above was similarly treated with benzoyl chloride to give colorless needles, m.p. $113-114^{\circ}$ alone and mixed with III.

(b).—To a solution of 230 mg. of lithium aluminum hydride in 5 cc. of dry ether, a solution of 2 g. of ethyl *dl-erythro-3-phenyl-2,3-dibromopropionate*¹⁰ (V) in 10 cc. of dry ether was added dropwise at 0° , and the reaction mixture kept at room temperature for 30 minutes and then boiled for an hour. The whole treatment was carried out with vigorous stirring. After cooling, ether and 10% sulfuric acid were added to the reaction mixture. The ether layer was washed with saturated sodium bicarbonate and then water, dried over anhydrous sodium sulfate and concentrated to leave an oily product. The oil was heated with 2 g. of benzoyl chloride at $130-140^{\circ}$ for two hours, and, after cooling, saturated sodium bicarbonate was added and the mixture allowed to stand for two days at room temperature. The mixture was extracted with ethyl acetate and the extract washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue crystallized by addition of methanol and recrystallized from ethanol, giving colorless needles, m.p. $113-115^{\circ}$ alone and on admixture with III derived from II. *Anal.* Calcd. for $C_{16}H_{14}O_2Br_2$: C, 48.27; H, 3.54. Found: C, 48.03; H, 3.55.

dl-erythro-3-Phenyl-2,3-dibromopropyl Benzimino Ether (VI) Hydrochloride.—A solution of 20 g. of II and 7 g. of benzonitrile in 10 cc. of dry ether was saturated with dry hydrogen chloride at 0° . A solid precipitated after standing in the cold for several days. The solid was collected, washed with dry ether and dried over sodium hydroxide *in vacuo*, to give 23.3 g. (79%) melting at $148-150^{\circ}$. *Anal.* Calcd. for $C_{16}H_{16}ONBr_2Cl$: N, 3.23. Found: N, 3.18.

An aqueous solution of VI hydrochloride was boiled for an hour to result in precipitation of colorless needles melting at $114-115^{\circ}$ and identical with III by a mixed m.p. determination.

dl-erythro-3-Phenyl-2,3-dibromopropyl Benzimino Ether (VI).—Twenty-six grams of VI hydrochloride was ground with 130 cc. of 10% sodium carbonate solution in a mortar for ten minutes and the solid was collected, washed with water and dried. Recrystallization from acetone gave colorless prisms, m.p. $133.5-135^{\circ}$, wt. 22 g. (92%). *Anal.* Calcd. for $C_{16}H_{16}ONBr_2$: C, 48.39; H, 3.81; N, 3.53. Found: C, 48.54; H, 3.77; N, 3.48.

dl-threo-2-Phenyl-4-phenylbromomethyl- Δ^2 -oxazoline (VII).—A mixture of 15 g. of VI and 30 g. of anhydrous sodium carbonate in 300 cc. of toluene was boiled with occasional shaking for an hour. After filtration, the pale yellow filtrate was concentrated *in vacuo* and with addition of small amounts of ether gave prisms, 10.3 g. (87%). After recrystallization from ether, it melted at $103-105^{\circ}$, $\lambda_{max}^{CCl_4}$ at 6.06μ . *Anal.* Calcd. for $C_{18}H_{14}ONBr$: C, 60.77; H, 4.46; N, 4.43. Found: C, 60.97; H, 4.20; N, 4.62.

Salts of *dl-threo-1-Benzoyloxy-2-amino-3-bromo-3-phenylpropane* (XII). (a) Hydrochloride.—To a solution of 4 g. of VII in 200 cc. of ether, a mixture of 5.5 cc. of 10% hydro-

chloric acid and 9 cc. of ethanol was added and the solution was kept at room temperature for several days. The precipitate was collected, washed with acetone and weighed, 4.5 g. (96%). Recrystallization from methanol gave colorless needles, m.p. $176-179^{\circ}$ dec., λ_{max}^{NaI} at 3.74, 3.85, 3.94, 5.81 and 6.57 μ . *Anal.* Calcd. for $C_{16}H_{17}O_2NBrCl$: C, 51.84; H, 4.62; N, 3.78. Found: C, 51.61; H, 4.29; N, 3.86.

(b) Hydrobromide.—Two grams of VII in 15 cc. of acetone was treated with 0.92 g. of 46% hydrobromic acid as described under (a) to yield 2 g. (76%) of XII hydrobromide. Recrystallization from methanol gave colorless needles, m.p. $190-192^{\circ}$ dec. *Anal.* Calcd. for $C_{16}H_{17}O_2NBr_2$: C, 46.29; H, 4.13; N, 3.37. Found: C, 46.28; H, 3.92; N, 3.31.

(c) Picrate.—A methanol solution of XII hydrochloride or hydrobromide was added to saturated sodium picrate to give a yellow precipitate. Recrystallization from methanol gave yellow plates which melted at $117-120^{\circ}$ after softening at 106° , but melted at $134-136^{\circ}$ after drying over phosphorus pentoxide *in vacuo* at 50° . *Anal.* Calcd. for $C_{22}H_{19}O_9N_4Br$: C, 46.90; H, 3.40; N, 9.95. Found: C, 47.10; H, 3.37; N, 9.64.

dl-threo-1-Phenyl-2-benzoylamino-1,3-dibromopropane (VIIIa). (a) From VII, with Oily By-product (B).—A solution of 500 mg. of VII in 5 cc. of dry benzene was saturated with dry hydrogen bromide and concentrated *in vacuo* to give an oily residue. The oil was boiled with 5 cc. of dry toluene for an hour. The solution was evaporated to dryness *in vacuo* to leave an oily residue which crystallized upon addition of a small volume of ethyl acetate. After filtration, it melted at $129-132^{\circ}$ and weighed 200 mg. (32%). Recrystallization from benzene gave colorless needles, m.p. $132-134^{\circ}$, λ_{max}^{NaI} at 3.11, 6.11 and 6.58 μ . *Anal.* Calcd. for $C_{16}H_{15}ONBr_2$: C, 48.39; H, 3.81; N, 3.53. Found: C, 48.05; H, 3.65; N, 3.50.

The ethyl acetate solution was concentrated to dryness to give an oily product (B) which gave IX hydrobromide, m.p. $206-208^{\circ}$ dec., 440 mg. (67%), by hydrolysis with 1% hydrobromic acid worked up exactly as in the case of oily product (A), below. *Anal.* Calcd. for $C_{16}H_{17}O_2NBr_2$: C, 46.29; H, 4.13; N, 3.37. Found: C, 46.70; H, 4.39; N, 3.48. Picrate: Recrystallization from methanol gave yellow prisms, m.p. $171-174^{\circ}$ which did not depress the m.p. on admixture with an authentic sample of IX picrate obtained by the procedure described below. *Anal.* Calcd. for $C_{22}H_{19}O_9N_4Br$: N, 9.95. Found: N, 9.75.

(b) From VI, with Oily By-product (A).—A solution of 1.6 g. of VI in 16 cc. of toluene was boiled for 1.5 hours and then worked up exactly as described under (a) to give VIIIa, m.p. $131-133^{\circ}$, wt. 200 mg. (13%) and a small amount of an oily product (A) which was converted to IX hydrochloride, m.p. $196-198^{\circ}$ dec., 320 mg. (22%), by hydrolysis with 10% hydrochloric acid. *Anal.* Calcd. for VIIIa, $C_{16}H_{15}ONBr_2$: C, 48.39; H, 3.81; N, 3.53. Found: C, 48.40; H, 3.85; N, 3.38.

Salts of *dl-threo-1-Phenyl-1-benzoyloxy-2-amino-3-bromopropane* (IX). (a) From VI via the Oily Product (A) Assumed to be *dl-erythro-1-Phenyl-2-benzoylamino-1,3-dibromopropane* (VIIIb).—Hydrobromide: (i) A solution of 8.1 g. of VI in 40 cc. of toluene was boiled for nine hours. At the beginning colorless needles¹¹ appeared and disappeared soon afterward. The toluene solution was evaporated to dryness *in vacuo* to give an oily product (A). This was heated in 16 cc. of 1% hydrobromic acid on a steam-bath for an hour with occasional shaking and crystals precipitated gradually while heating. The crystals were filtered, washed with acetone and dried, 4.5 g. (53%). Recrystallization from water gave colorless needles, m.p. $206-208^{\circ}$ dec. *Anal.* Calcd. for $C_{16}H_{17}O_2NBr_2$: C, 46.29; H, 4.13; N, 3.37. Found: C, 46.55; H, 3.89; N, 3.24.

The acetone solution was concentrated to leave a solid. Recrystallization from methanol gave colorless leaflets of *dl-erythro-1-phenyl-1,2,3-tribromopropane* (XI),⁹ m.p. $123.5-125.5^{\circ}$, 1 g. *Anal.* Calcd. for $C_9H_5Br_3$: C, 30.28; H, 2.54. Found: C, 30.43; H, 2.57.

(ii) When 95% ethanol was used in place of 1% hydro-

(8) All melting points are uncorrected.

(9) E. Grimaux, *Bull. soc. chim.*, **2**, 20, 120.

(10) J. J. Sudborough and K. J. Thompson, *J. Chem. Soc.*, **83**, 671 (1903).

(11) A pinch of the material was separated and proven to be VI hydrobromide by microanalysis and by the fact that the base derived from it was identical with VI. *Anal.* Calcd. for VI hydrobromide, $C_{16}H_{16}ONBr_2$: N, 2.93. Found: N, 3.0.

bromic acid for hydrolysis, IX hydrobromide was also obtained.

Hydrochloride: The substitution of 10% hydrochloric acid for 1% hydrobromic acid in the hydrolysis of oil (A) gave rise to IX-hydrochloride. Recrystallization from a mixed solvent of ethyl acetate and methanol gave colorless silky needles, m.p. 194–196° dec. *Anal.* Calcd. for $C_{16}H_{17}O_2NBrCl$: C, 51.84; H, 4.62; N, 3.78. Found: C, 52.06; H, 4.43; N, 3.64.

Picrate: Recrystallization from methanol gave yellow prisms, m.p. 171–173°. *Anal.* Calcd. for $C_{22}H_{19}O_9N_4Br$: C, 46.90; H, 3.40; N, 9.95. Found: C, 46.68; H, 3.41; N, 9.87.

(b) From VIIIa via the Oily Product (C) Assumed to be VIIIb.—Hydrobromide: (i) A solution of 200 mg. of VIIIa in 10 cc. of dry toluene was boiled for six hours and evaporated to dryness *in vacuo* to leave an oily product (C). The oil (C) was heated in 1 cc. of 1% hydrobromic acid on a steam-bath for an hour to deposit a solid gradually. The solid was washed with hot benzene to give colorless needles, 130 mg. (63%). After recrystallization from water, it melted at 206–208° dec. *Anal.* Calcd. for $C_{16}H_{17}O_2NBr_2$: C, 46.29; H, 4.13; N, 3.37. Found: C, 46.22; H, 4.11; N, 3.47.

(ii) When toluene used in procedure (i) was saturated with dry hydrogen bromide and then worked up exactly as the manner of (i), the yield of IX hydrobromide was 73%, superior to that of (i). The picrate melted at 172–174° and showed no depression of m.p. on admixture with an authentic sample of IX picrate. *Anal.* Calcd. for $C_{22}H_{19}O_9N_4Br$: N, 9.95. Found: N, 10.22.

Reduction of dl-threo-1-Phenyl-1-benzoyloxy-2-amino-3-bromopropane (IX) Hydrobromide to Give dl-ψ-N-Benzoylnorephedrine (X).—IX Hydrobromide (500 mg.) was added to a pre-reduced suspension of 500 mg. of 20% palladium-charcoal in 50 cc. of methanol and the mixture hydrogenated at 25–30° under atmospheric pressure. More than 0.8 mole of hydrogen per mole of IX hydrobromide was absorbed during several days. The methanolic filtrate was concentrated to dryness to leave a solid residue which was then dissolved in hot water, and made alkaline by adding sodium bicarbonate. An oily product precipitated and crystallized gradually. Recrystallization from a mixed solvent of ether and petroleum ether gave colorless needles, m.p. 126–128°, alone and on admixture with an authentic sample of dl-ψ-N-benzoylnorephedrine.⁹ *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.01; H, 6.19; N, 5.63.

Hydrolysis of dl-threo-1-Phenyl-2-benzoylamino-1,3-dibromopropane (VIIIa) in Aqueous Solvents. (a) **In Cold 90% Ethanol Containing 0.1% Hydrobromic Acid.**—Formation of salts of dl-threo-1-benzoyloxy-2-amino-3-bromo-3-phenylpropane (XII). A solution of 500 mg. of VIIIa in 50 cc. of 90% ethanol containing 0.1% hydrobromic acid was allowed to stand at room temperature for two weeks. The solution was evaporated *in vacuo* to dryness to give a solid, washed with ether and weighed, 420 mg. (80%). Recrystallization from methanol gave large colorless needles, m.p. 191–194° dec. *Anal.* Calcd. for XII hydrobromide, $C_{16}H_{17}O_2NBr_2$: C, 46.29; H, 4.13; N, 3.37. Found: C, 46.29; H, 3.76; N, 3.58.

A methanolic solution of the needles was added to a saturated aqueous solution of sodium picrate to give a yellow solid. Recrystallization from methanol gave yellow plates, wt. 500 mg. (70%). It melted at 117–120° after softening at 106°, but melted at 133–135° after drying over phosphorus pentoxide *in vacuo* at 50° and showed no depression on admixture with XII picrate derived from VII. *Anal.* Calcd. for $C_{22}H_{19}O_9N_4Br$: N, 9.95. Found: N, 9.79.

(b) **In Hot 99% Ethanol Containing 0.1% Hydrobromic Acid.**—Formation of salts of dl-threo-1-phenyl-1-benzoyloxy-2-amino-3-bromopropane (IX) and dl-threo-1-benzoyloxy-2-amino-3-bromo-3-phenylpropane (XII): A solution of 500

mg. of VIIIa in 50 cc. of 99% ethanol containing 0.1% hydrobromic acid was boiled for six hours. After concentration *in vacuo*, the remaining solid weighed 380 mg. and recrystallized from water to give colorless needles, m.p. 192–193° dec. The needles were converted to picrate by the usual method and after successive recrystallization from methanol divided to give two types of picrate, yellow prisms of m.p. 172–174°, wt. 60 mg. (8.5%), and yellow plates of m.p. 133–135° (after drying over phosphorus pentoxide), wt. 230 mg. (32.4%). The former picrate was less soluble in methanol, positive in the Beilstein halogen test and showed no depression of m.p. on admixture with IX picrate. *Anal.* Calcd. for $C_{22}H_{19}O_9N_4Br$: N, 9.95. Found: N, 9.59.

The latter picrate was positive in the halogen test and melted at 117–120° after softening at 106°, whilst at 133–135° after drying over phosphorus pentoxide, alone and on admixture with XII picrate. *Anal.* Calcd. for $C_{22}H_{19}O_9N_4Br$: N, 9.95. Found: N, 9.82.

When to the aqueous mother liquor of recrystallization of the reaction product was added a saturated aqueous solution of sodium picrate, a third picrate was obtained, and recrystallization from methanol gave yellow needles, m.p. 175–177°. This picrate was negative in the halogen test and analysis indicated the empirical formula $C_{22}H_{20}O_{10}N_4$. But it was not identical with picrates of dl-threo-1-phenyl-1-benzoyloxy-2-aminopropan-3-ol¹² or dl-threo-1-phenyl-2-amino-3-benzoyloxypropan-1-ol¹² by mixed m.p. determinations. These observations guided us to the supposition that it would be the picrate of dl-erythro-1-phenyl-1-benzoyloxy-2-aminopropan-3-ol, though its characterization failed and will be tried in future. *Anal.* Calcd. for $C_{22}H_{20}O_{10}N_4$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.70; H, 4.18; N, 11.31.

dl-threo-1-Phenyl-2-benzoylamino-1,3-propanediol (XIII). (a)—A solution of 500 mg. of IX hydrobromide in 50 cc. of water was boiled for four hours; the pH of the solution changed from 5.4 to 1.6. The solution was concentrated *in vacuo* to a small volume, and made alkaline with 10% sodium hydroxide solution to give an oily product which then crystallized, wt. 240 mg. (73%). Recrystallization from ethyl acetate gave colorless needles, m.p. 163–165°, and not depressed on admixture with an authentic sample of dl-threo-1-phenyl-2-benzoylamino-1,3-propanediol.¹³ *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.77; H, 5.98; N, 4.80.

(b)—A solution of 2 g. of VI in 20 cc. of toluene was boiled for five hours, and concentrated *in vacuo* to dryness to give an oily product (A). A solution of the residue (A) in 200 cc. of water was boiled for five hours and concentrated *in vacuo* to a small volume, and washed with ethyl acetate. The water layer was made alkaline with 10% sodium hydroxide solution to cause separation of an oily product, which solidified gradually. The solid was collected and recrystallized from ethyl acetate to give 290 mg. (21%) of colorless needles, m.p. 158–163°, alone and on admixture with an authentic sample of XIII.

Acknowledgments.—We wish to express our gratitude to Dr. M. Miyamoto of the Takeda Co. for the gift of a specimen of dl-threo-1-phenyl-2-benzoylamino-1,3-propanediol and to the Shinagawa Factory of the Sankyo Co. for supplying the *trans*-cinnamic alcohol. Our thanks are also due to the Microanalytical Sections of this Institute and the Sankyo Co. for the microanalyses and to the Technical Department of the Tokyo University and the Asahikasei Co. for the infrared spectra determinations.

KATAKASU, FUKUOKA, JAPAN

(12) They will be reported in a subsequent paper.

(13) M. Miyamoto, *J. Pharm. Soc. Japan*, **72**, 677 (1952).