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16. Tanezo Taguchi, Munemitsu Tomoeda, and Haruki Fukuyama : Studies in Stereochemistry. IX. *dl*-Phenylserinols : A New Synthesis and its Stereochemical Findings. (2)[1]

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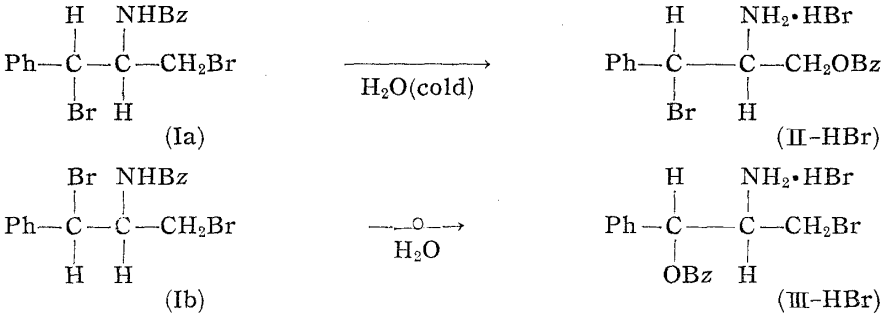
The acyl group of monoacylated *dl*-phenylserinols may migrate between the three functional groups, C_1-OH, C_2-NH_2, and C_3-OH. Accordingly, when two bromine atoms of *dl*-1-phenyl-2-acylamino-1,3-dibromopropanes are stepwise replaced by hydroxyl groups, it is supposed that acyl participation is affected by the relative situation of the bromine atoms and acyl group. The purpose of this report is to clarify this problem in connection with the foregoing paper.[1] We have reported that in the partial hydrolysis of *dl-threo*-1-phenyl-2-benzoylamino-1,3-dibromopropane (Ia), acyl participation at C_3 was preferred over participation at C_1 to yield *dl-threo*-1-phenyl-1-bromo-2-amino-3-benzoyloxypropane (II) hydrobromide, but in the similar hydrolysis of the *erythro* isomer (Ib), acyl participation at C_1 was preferred over that at C_3 to yield *dl-threo*-1-phenyl-1-benzoyloxy-2-amino-3-bromopropane (III) hydrobromide.



The oily free base (III), liberated from its hydrobromide by treatment with sodium bicarbonate, was heated in benzene and there appeared a precipitate which was identical with the hydrobromide. The benzene solution was evaporated to give prisms which were characterized as *dl*-2-phenyl-4-phenylhydroxymethyl-Δ^2-oxazoline (IV) by microanalytical data and infrared spectra, and designated as *threo* because its formation reaction does not involve the breaking of any bonds to asymmetric carbon atoms. It may be due to the formation of a hydrogen bond between nitrogen of the oxazoline ring and hydrogen of C_1-hydroxyl that the shift of the hydroxyl absorption to the side of longer wave lengths was found in its infrared spectrum. The precipitation of (III) hydrobromide seems to occur by recombination of the rest of (III) with hydrogen bromide liberated by the oxazoline (IV) formation via *dl-threo*-1-phenyl-2-benzoylamino-3-bromopropan-1-ol.

On treatment in aqueous media, (IV) hydrochloride or picrate added one mole of water to convert into the corresponding salts of *dl-threo*-1-phenyl-2-amino-3-benzoyloxypropan-1-ol (V) which were then treated with caustic soda to yield *dl-threo*-1-phenyl-2-benzoylaminopropane-1,3-diol (VI) with acyl migration from oxygen to nitrogen. Then, in anticipation of the reverse N→O acyl migration, (VI) was treated with dry hydrogen chloride in ethanol and the resulting O-acylamino hydrochloride was not the hydrochloride of (V) but of *dl-threo*-1-phenyl-1-benzoyloxy-2-aminopropan-3-ol (VII) which gave (VI) again on treatment with caustic soda. Thus, it was shown that

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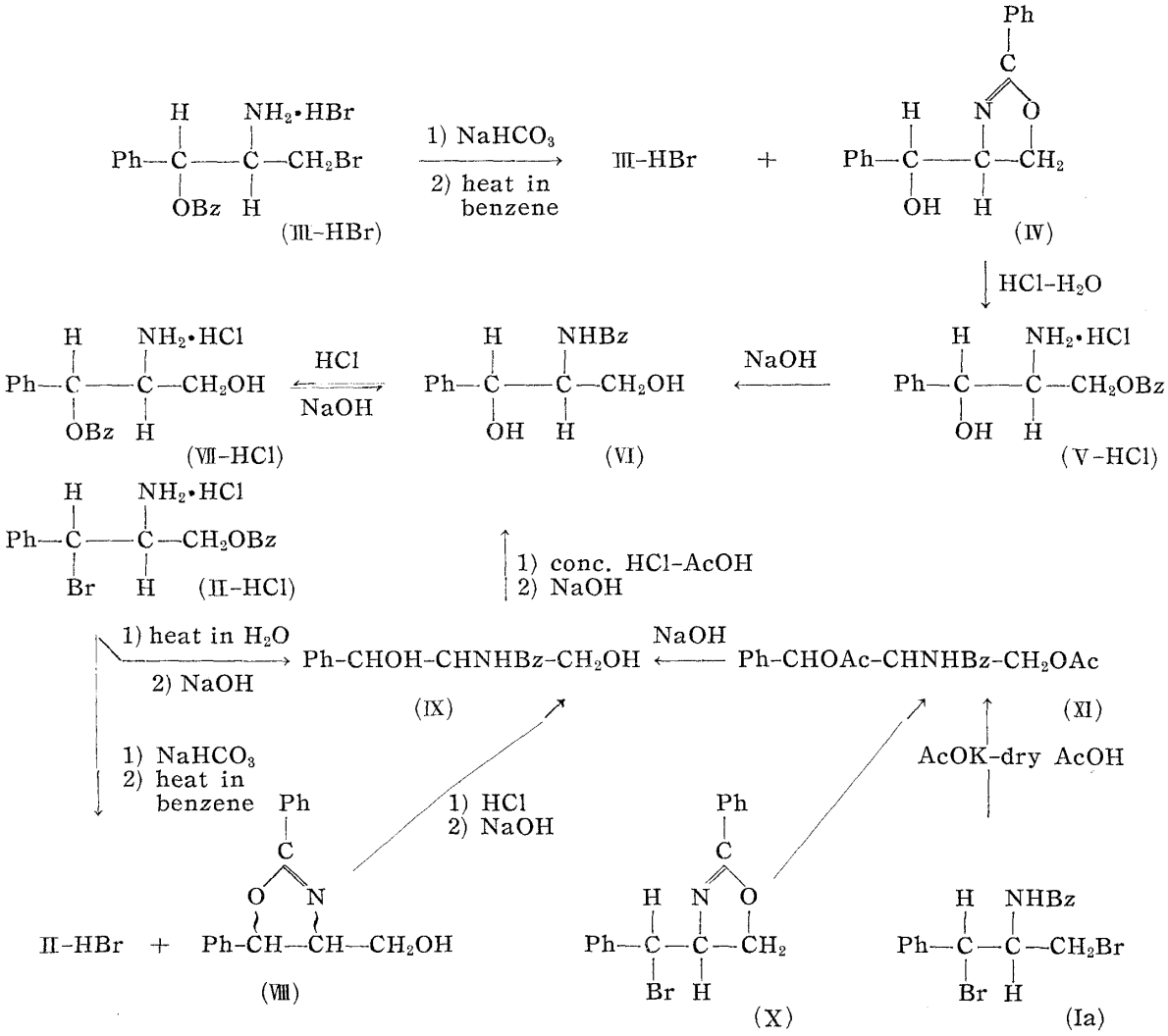
in the *dl-threo*-acylaminopropanediol (VI), the acyl migration from nitrogen to C_1-OH took preference over that from nitrogen to C_3-OH.

dl-threo-1-Phenyl-1-bromo-2-amino-3-benzoyloxypropane (II) was liberated from its hydrochloride with sodium bicarbonate and heated in benzene to precipitate (II) hydrobromide. On evaporation of the benzene solution the resulting prisms melted at 145~147°, comparative sharply, in agreement with m.p. 148° of *dl-erythro*-2-phenyl-4-hydroxymethyl-5-phenyl-Δ^2-oxazoline reported by Viscontini *et al.*[2] and, except for the configurational decision, the structure of the former was proved to be the same with that of the latter by microanalytical data and infrared spectra. However, on treatments with hydrochloric acid followed by caustic soda the former did not give pure *dl-erythro*-1-phenyl-2-benzoylaminopropane-1,3-diol, but gave a mixture of *dl-threo*-and-*erythro*-1-phenyl-2-benzoylaminopropane-1,3-diol (IX) whose structure was deduced from the fact that the mixture was converted entirely to (VI) on treatments with hydrochloric acid in acetic acid followed by caustic soda. The deduction was derived from the fact that, as has often been experienced[1,3] in the N→O acyl migration of N-acyl-*dl*-phenylserinols by treatment with hydrochloric and acetic acids, the *erythro* isomer is furnished by inversion but the *threo* isomer is not. Accordingly, the oxazoline in question was also supposed to consist of a mixture of *erythro* and *threo*



2) M. Viscontini, E. Fuchs: Helv. Chim. Acta, **36**, 1(1953).
3) M. Miyamoto: J. Pharm. Soc. Japan, **72**, 677(1952).

forms (VIII). Furthermore, the formation of the oxazoline mixture from (II), it is assumed, originated from the supposed epimerization of a portion of *dl-threo*-1-phenyl-1-bromo-2-benzoylaminopropan-3-ol, which was formed from (II) as a result of O→N acyl migration, to its *erythro* isomer by heat. The supposition of the epimerization seems to be reasonable from the fact that (Ia) undergoes epimerization to (Ib) by heat.[1]

When the hydrochloride of (II) was boiled in water, it showed rapid decrease of pH of the solution and gave rise to a mixture of *dl-threo*- and *-erythro*-1-phenyl-2-benzoylaminopropane-1,3-diol (IX) on making alkaline, the constructional proof for which was made, similarly as mentioned above, by their entire derivation to N-benzoyl-*dl-threo*-phenylserinol (VI) on treatment with hydrochloric and acetic acids, followed by caustic soda. The reason why N-benzoyl-*dl-threo*-phenylserinol was contaminated with the *erythro* epimer may be due to the fact that the reaction proceeded through Sn_1 mechanism because of the absence of possibility of acyl participation in (II) hydrochloride.

It is interesting that in this series of compound the replacement of bromine atom by acetoxyl group in the dry condition is compared with the replacement of bromine atom with a hydroxyl group in a moist condition. For this purpose (Ia) was treated with dry acetic acid and potassium acetate to give a mixture of diacetyl-monobenzoyl-*dl-threo*- and *-erythro*-phenylserinols (XI). The structure of the reaction product was also proved by its entire conversion to benzoyl-*dl-threo*-phenylserinol (VI) through a mixture of N-benzoyl-*dl-threo*- and *-erythro*-phenylserinols (IX) as mentioned above. On the other hand, the same treatment of *dl-threo*-2-phenyl-4-phenylbromomethyl-Δ^2-oxazoline (X) also gave an analogous result. From the latter observation, it is assumed that these reactions proceed through either less possible Sn_1 mechanism or more possible Sn_2, accompanied with a partial epimerization of C_1-Br by heat, but it is not clear which is correct until further evidences are accumulated.

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Experimental

***dl-threo*-2-Phenyl-4-phenylhydroxymethyl-Δ^2-oxazoline (IV)**—MeOH solution of 2.0 g. of (III) hydrobromide was added to a dil. aq. solution of 2.0 g. of $NaHCO_3$ and the precipitated oil was extracted with 60 cc. of benzene. The extract was washed with water and dried over anhyd. Na_2SO_4. The benzene soultion was heated on a steam bath and the colorless silky needles that precipitated out were collected. After recrystallization from water, it melted at 206~208°(decomp.); yield, 880 mg. *Anal.* Calcd. for $C_{16}H_{17}O_2NBr_2$ ((III) hydrobromide) : C, 46.29; H, 4.13; N, 3.37. Found: C, 46.60; H, 4.23; N, 3.66.

Picrate : Recrystallization from MeOH gave yellow prisms, m.p. 171~173°, alone and on admixture with an authentic sample of (III) picrate[1].

Concentration of the benzene filtrate followed by addition of small amounts of ether[4] gave colorless prisms. After recrystallization from EtOH, it melted at 125~127°; yield, 350 mg. $\lambda_{max}^{Hexachlorobutadiene}$: 3.21 and 6.07 μ. *Anal.* Calcd. for $C_{16}H_{14}O_2N$ (IV) : C, 75.87; H, 5.97; N, 5.53. Found : C, 75.72; H, 5.90; N, 5.68.

To dehyd. ether solution of the prisms, a saturated dehyd. ether solution of picric acid was added and yellow needles precipitated. After recrystallization from abs. EtOH, it melted at 139~141°. *Anal.* Calcd. for $C_{22}H_{18}O_9N_4$((IV)-picrate) : N, 11.62. Found : N, 11.72.

Salts of *dl-threo*-1-Phenyl-2-amino-3-benzoyloxypropan-1-ol (V)—Hydrochloride : A solution of 300 mg. of (IV) in a mixture of 0.3 cc. of conc. HCl and 30 cc. of EtOH was heated on a steam bath for 10 mins. and concentrated *in vacuo*. The crystals were recrystallized from acetone to

4) After separating prisms (IV), another lot of colorless needles were obtained from the ether solution. It melted at 158~160° and the microanalytical data were as follows : C, 75.66; H, 5.89. Its molecular structure will be reported in a subsequent paper.

colorless prisms, m.p. 168~170°; yield 200 mg. *Anal.* Calcd. for $C_{16}H_{18}O_3NCl$ ((V) hydrochloride): C, 62.43; H, 5.89; N, 4.55. Found: C, 62.25; H, 6.15; N, 4.75.

Picrate: A solution of 300 mg. of (IV)-picrate in 10 cc. of 90% EtOH was heated for 2 hrs. on a steam bath and allowed to stand over night at room temperature. The solution was concentrated *in vacuo*. The yellow crystals were recrystallized from 50% EtOH to yellow needles, m.p. 166~168°; yield, 310 mg. *Anal.* Calcd. for $C_{22}H_{20}O_{10}N_4$ ((V) picrate): C, 52.80; H, 4.03; N, 11.20. Found: C, 52.62; H, 3.79; N, 10.98.

Salts of *dl-threo*-1-Phenyl-1-benzoyloxy-2-aminopropan-3-ol (VII)—Hydrochloride: A solution of 70 mg. of (VI) in 30 cc. of abs. EtOH was saturated with dry HCl at 0° and kept in the cold over night. Concentration of the solution *in vacuo* and recrystallization of the solid residue from a mixture of MeOH and ether gave colorless silky needles, m.p. 191~193°(decomp.), which depressed the m.p. of (V) hydrochloride on admixture. *Anal.* Calcd. for $C_{16}H_{18}O_3NCl$ ((VII) hydrochloride): C, 62.43; H, 5.89; N, 4.55. Found: C, 62.60; H, 6.09; N, 4·49.

Picrate: Recrystallization from 50% EtOH gave yellow needles, m.p. 175~177°, which depressed the m.p. of (V) picrate on admixture. *Anal.* Calcd. for $C_{22}H_{20}O_{10}N_4$ (VII picrate): C, 52.80; H, 4.03; N, 11.20. Found: C, 53.04; H, 3.72; N, 11.15.

A Mixture of *dl-threo*- and *-erythro*-2-Phenyl-4-hydroxymethyl-5-phenyl-Δ^2-oxazoline (VIII)—MeOH solution of 1.88 g. of (II)-hydrochloride was added to a dil. aq. solution of $NaHCO_3$ and the precipitated oil was extracted with 60 cc. of benzene, which was washed with water and dried over anhyd. Na_2SO_4. The benzene solution was heated on a steam bath and the colorless silky needles that precipitated were collected. After recrystallization from water, it melted at 190~192° (decomp.); yield, 650 mg. *Anal.* Calcd. for $C_{16}H_{17}O_2NBr_2$ ((II)-hydrobromide): C, 46.29; H, 4.13; N, 3.37. Found: C, 46.73; H, 4.01; N, 3.34.

Picrate: Recrystallization from MeOH gave yellow plates, m.p. 133~135°, after drying over P_2O_5, alone and on admixture with an authentic sample of II-picrate[2].

Concentration of the filtrate, followed by addition of small amounts of ether gave colorless prisms. After recrystallization from EtOH it melted at 145~147°. $\lambda_{max}^{Hexachlorobutadiene}$: 3.13 and 6.11 μ; yield, 150 mg. *Anal.* Calcd. for $C_{16}H_{14}O_2N$ (VIII): C, 75.86; H, 5.97; N, 5.53. Found: C, 75.96; H, 6.20; N, 5.55.

A Mixture of *dl-threo*- and *-erythro*-1-Phenyl-2-benzoylamino-1,3-diacetoxypropane (XI)—a) From (X): A solution of 1.0 g. of (X) and 0.96 g .of anhyd. AcOK in a mixture of 4 cc. of Ac_2O and 16 cc. of AcOH was boiled for 10 hrs., cooled, and poured into ice water. Several recrystallization of the solid precipitate from AcOEt gave colorless needles, m.p. 166~167.5°; yield, 350 mg. *Anal.* Calcd. for $C_{20}H_{21}O_5N$ (XI): C, 67.59; H, 5.96; N, 3.94. Found: C, 67.34; H, 5.96; N, 4.07.

b) From (Ia): A solution of 1.0 g. of (Ia) and 1.0 g. of anhyd. AcOK in a mixture of 5 cc. of Ac_2O and 15 cc. of AcOH was boiled for 10 hrs. and concentrated *in vacuo*. The residue was extracted with AcOEt, washed with sat. $NaHCO_3$ solution, then with water, and dried over anhyd. Na_2SO_4. AcOEt solution was concentrated *in vacuo*, followed by the addition of a small amount of ether and gave colorless needles. After recrystallization from benzene it melted at 166~167.5°, alone and on admixture with a sample obtained by procedure (a); yield, 320 mg. *Anal.* Calcd. for $C_{20}H_{21}O_5N$(XI): N, 3.94. Found: N, 4.32.

***dl-threo*-1-Phenyl-2-benzoylaminopropane-1,3-diol (VI)**—a) From (V) hydrochloride or picrate: A solution of 110 mg. of (V) hydrochloride in 2 cc. of water was made alkaline with 10% NaOH and an oily product precipitated, which then crystallized. Recrystallization from AcOEt gave colorless needles, m.p. 163~165°, alone and on admixture with an authentic sample[2]; yield, 80 mg. *Anal.* Calcd. for $C_{16}H_{17}O_3N$ (VI): N, 5.16. Found: N, 5.55,

Treatment of 120 mg. of (V) picrate with alkali just like the hydrochloride gave 50 mg. of (VI).

b) From (VII) hydrochloride: A solution of 30 mg. of (VII) hydrochloride in 3 cc. of water was made alkaline with 10% NaOH and an oily product precipitated, which later crystallized. Recrystallization from AcOEt gave colorless needles, m.p. 163~165°, alone and on admixture with an authentic sample of (VI), yield 20 mg.

c) From (II)-hydrochloride via a mixture of *dl-threo*- and *-erythro*-1-phenyl-2-benzoylaminopropane-1,3-diol (IX): A solution of 1.0 g. of (II) hydrochloride in 100 cc. of water was boiled for 5 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 give an oily product, which then crystallized. Recrystallization from AcOEt gave colorless needles, m.p. 130°; yield, 480 mg. *Anal.* Calcd. for $C_{16}H_{17}O_3N$(IX): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.45; H, 6.50; N, 5.30.

A solution of 120 mg. of the foregoing needles in a mixture of 0.4 cc. of conc. HCl and 0.8 cc. of AcOH, boiled for 5 mins., and concentrated *in vacuo*. The solid residue was dissolved in hot water 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 (VI); yield, 60 mg. *Anal.* Calcd. for $C_{16}H_{17}O_3N$ (VI): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.57; H, 6.00; N, 5.24.

d) From (VIII) via a mixture of *dl-threo-* and *-erythro-*1-phenyl-2-benzoylaminopropane-1,3-diol (IX): A solution of 170 mg. of (VIII) in a mixture of 0.2 cc. of conc. HCl, 0.3 cc. of water, and 10 cc. of EtOH was heated on a steam bath for 1.5 hrs. The solution was concentrated *in vacuo* to a small volume and made alkaline with 10% NaOH to give an oil, which then crystallized. Recrystallization from AcOEt gave colorless needles (IX), m.p. 128~130°; yield, 170 mg. *Anal.* Calcd. for $C_{16}H_{17}O_3N$ (IX): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.87; H, 6.34; N, 5.62.

A solution of 220 mg. of the needles in a mixture of 0.6 cc. of conc. HCl and 1.2 cc. of AcOH was boiled for 5 mins. and concentrated *in vacuo* to a small volume. The solution was 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 (VI); yield, 150 mg. *Anal.* Calcd. for $C_{16}H_{17}O_3N$ (VI): N, 5.16. Found: N, 5.27.

e) From (XI) via a mixture of *dl-threo-* and *-erythro-*1-phenyl-2-benzoylaminopropane-1,3-diol (IX): i) A solution of 1.2 g. of (XI)(derived from (X)), 270 mg. of NaOH in 30 cc. of 50% MeOH was heated on a steam bath for 1 hr. and concentrated *in vacuo* to a small volume to yield a solid precipitate. Recrystallization from AcOEt gave colorless needles (IX), m.p. 126~130°; yield, 600 mg.

The needle crystals were boiled in a mixture of 1.8 cc. of conc. HCl and 3.6 cc. AcOH for 5 mins. The solution was concentrated *in vacuo* to a small volume 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 (VI); yield, 550 mg.

ii) A solution of 200 mg. of (XI)(derived from (Ia)) and 50 mg. of NaOH in 20 cc. of 90% MeOH was heated on a steam bath for 1 hr. and concentrated *in vacuo* to yield a solid precipitate. The solid was extracted with AcOEt, washed with water, dried over anhyd. Na_2SO_4, and concentrated to give crystals. Recrystallization from AcOEt gave colorless needles (IX), m.p. 126~130°; yield, 110 mg.

The needle crystals were boiled in a mixture of 0.25 cc. of conc. HCl and 0.5 cc. of AcOH for 7 mins. The solution was concentrated *in vacuo* to a small volume and made alkaline with 10% NaOH to give an oily product, which then crystallized. Recrystallization form AcOEt gave colorless needles, m.p. 164~165°, alone and on admixture with an authentic sample of (VI); yield, 60 mg.

Summary

In the derivation of *dl*-1-phenyl-2-acylamino-1,3-dibromopropanes to *dl*-phenylserinols, the stepwise displacement of bromine atoms by hydroxyl groups was examined in connection with earlier conclusions. It was found that the proximity of acyl group to the displacement centre favored the internal Sn_2 and that its distance from the neighborhood favored Sn_1 in the solvolytic condition.

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