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88. Tanezo Taguchi and Munemitsu Tomoeda : Studies in Stereochemistry. X. *dl*-Phenylserinols : A New Synthesis and its Stereochemical Findings. (3).[1] Ring Opening of *dl-threo*-2-Phenyl-4-phenylhydroxymethyl-Δ^2-oxazoline in Basic Media.

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In the preceding paper of this series,[1] it was shown that *dl-threo*-1-phenyl-1-benzoyloxy-2-amino-3-bromopropane (I), liberated from its hydrobromide with sodium hydrogen carbonate, when boiled in benzene, yielded an N-containing colorless needles (A) as a minor product in accompaniment with the formation of *dl-threo*-2-phenyl-4-phenylhydroxymethyl-Δ^2-oxazoline (II), which was formed from (I) through successive migration and participation of the benzoyl radical. The purpose of this report lies in the identification of the product (A) and discussion of its formation mechanism.

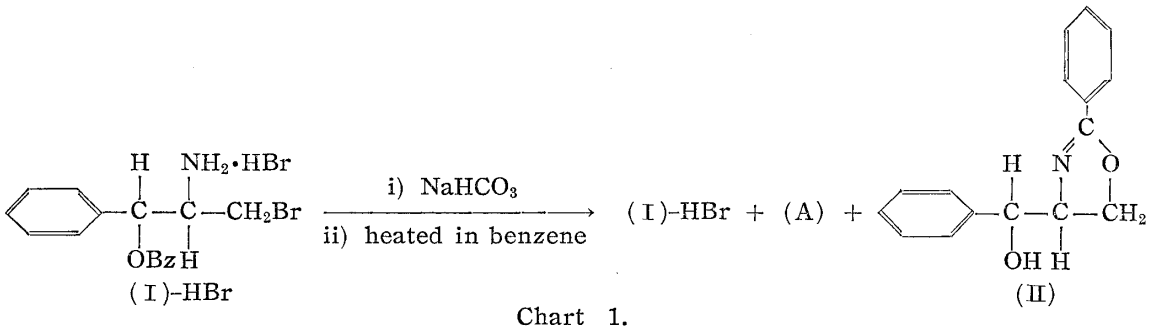

Chart 1.

The product (A) was formed also on heating hydrobromide of (I) in the following three media : a) In 90% EtOH with AcOK where *dl-threo*-1-phenyl-2-benzoylaminopropane-1, 3-diol (III) was obtained in nearly the same yield; b) in dehydrated EtOH with anhyd. Na_2CO_3; and c) in 90% MeOH containing 1% NaOH where (II) was obtained in a quantity twice that of (A).

The data of microanalysis and molecular weight determination indicated $C_{16}H_{15}O_2N$ for the product (A), showing it to be in accordance with oxazoline (II) only in empirical formulation. (A) was soluble in dilute mineral acids, but neither its hydrochloride nor picrate could be isolated, suggesting the existence of an alcohol and N-benzoyl groups. On hydrogenation, (A) absorbed about one mole of hydrogen to give *dl*-1-phenyl-2-benzoylaminopropan-3-ol (V), which was identified with an authentic sample derived from *dl*-1-phenyl-2-aminopropan-3-ol (VI) hydrochloride[2] by benzoylation. Besides, the comparison of ultraviolet spectra of (A) and (V) suggested the existence of a stronger conjugated system of double bonds in the structure of (A). On these experimental bases, the structure of (A) was concluded to be *dl*-1-phenyl-2-benzoylaminoprop-1-en-3-ol (IVa) or *dl*-1-phenyl-2-benzoyliminopropan-3-ol (IVb). Infrared spectrum supports the (IVb) form for both the structures, but the existence of either >C=C(NHBz)- or >CH-C(=NBz)-, as Alberti has suggested,[3] cannot be rigidly proved only by infrared spectrum. Therefore, it may be possible that the structure of (A) could be shown alternately by both structures.

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1) Part (2). T. Taguchi, M. Tomoeda, H. Fukuyama : This Bulletin, **4**, 80(1956).
2) S. Ikuma, M. Nagawa : J. Pharm. Soc. Japan, **72**, 310(1952).
3) C. G. Alberti, *et al.* : Gazz. chim. ital., **84**, 519(1954).

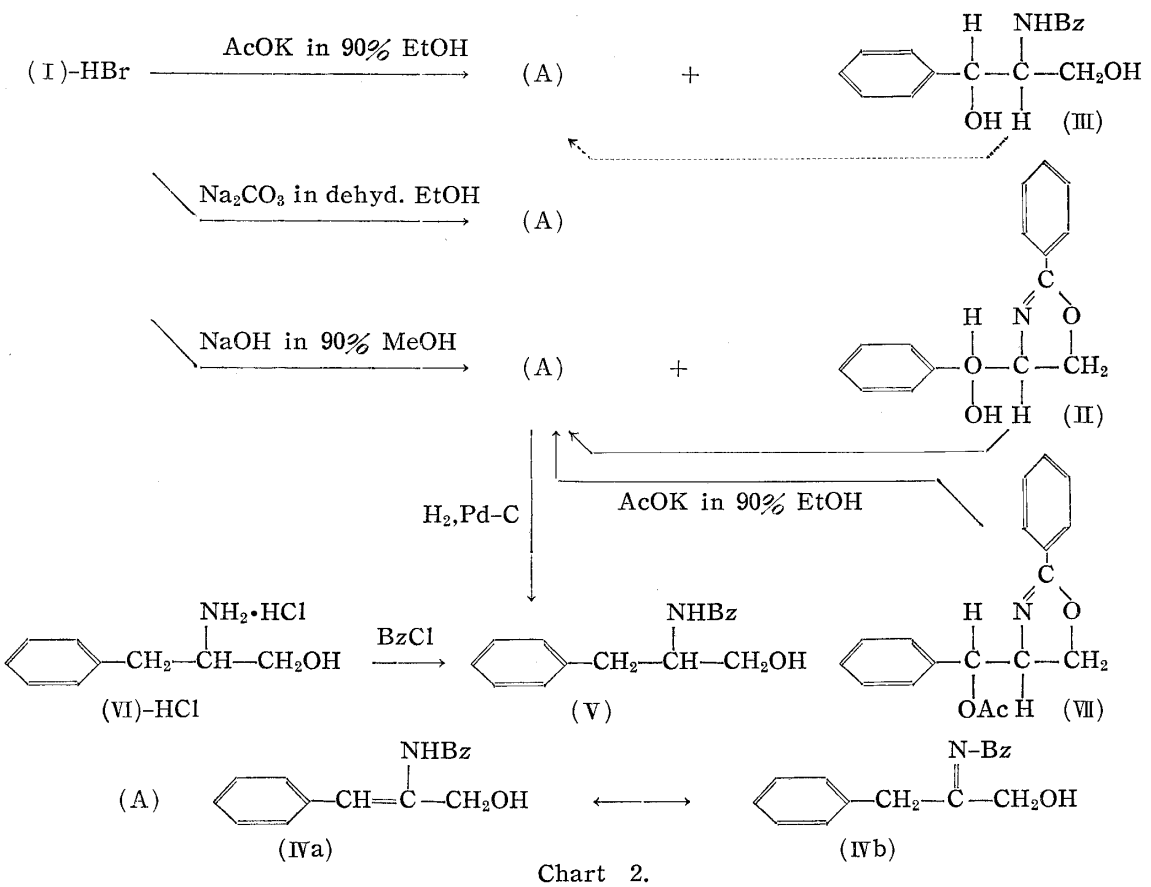

Chart 2.

It is worth noting that on treatment of (II) or (III) in basic and also neutral media, (A) was obtained only from (II). This fact shows that (III), when formed, cannot be converted into (IV). (IV) was derived also from *dl-threo*-2-phenyl-4-phenylacetoxymethyl-Δ^2-oxazoline (VII)[4] on treatment with AcOK in 90% EtOH.

From these data it was presumed that the reaction course on treatment of (I) hydrobromide in basic medium proceeds through the routes shown in Chart 3. a) One route via oxazolidinium cation in transition state results in formation of (III) and b) the other course via oxazolinium cation results in formation of (IV). The process from (II) to (IV) is discussed in detail as follows: The elimination of water did not occur under the same conditions from (III), which corresponds theoretically to (II) with one mole of water added. Therefore, it is deduced that the formation of (IV) from (II) starts with the elimination of water followed by ring opening. The deduction is further supported from the consideration that the initial elimination of water may occur easily, because infrared spectrum shows the existence of strong hydrogen bond between H of OH group and N in the molecule of (II), and accordingly OH and C_4–H are in *trans*.

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Experimental

Formation of *dl*-1-Phenyl-2-benzoylaminoprop-1-en-3-ol (or *dl*-1-Phenyl-2-benzoyliminopropan-3-ol) (IV)—a) From *dl-threo*-1-Phenyl-1-benzoyloxy-2-amino-3-bromopropane (I) Hydrobromide: 1) With AcOK in 90% EtOH; Simultaneous Formation of *dl-threo*-1-Phenyl-2-benzoylaminopropane-1,3-diol (III): A solution of 2.0 g. of (I)-HBr and 4 g. of anhyd. AcOK in 60 cc. of 90% EtOH was

4) Will be reported in a subsequent paper.

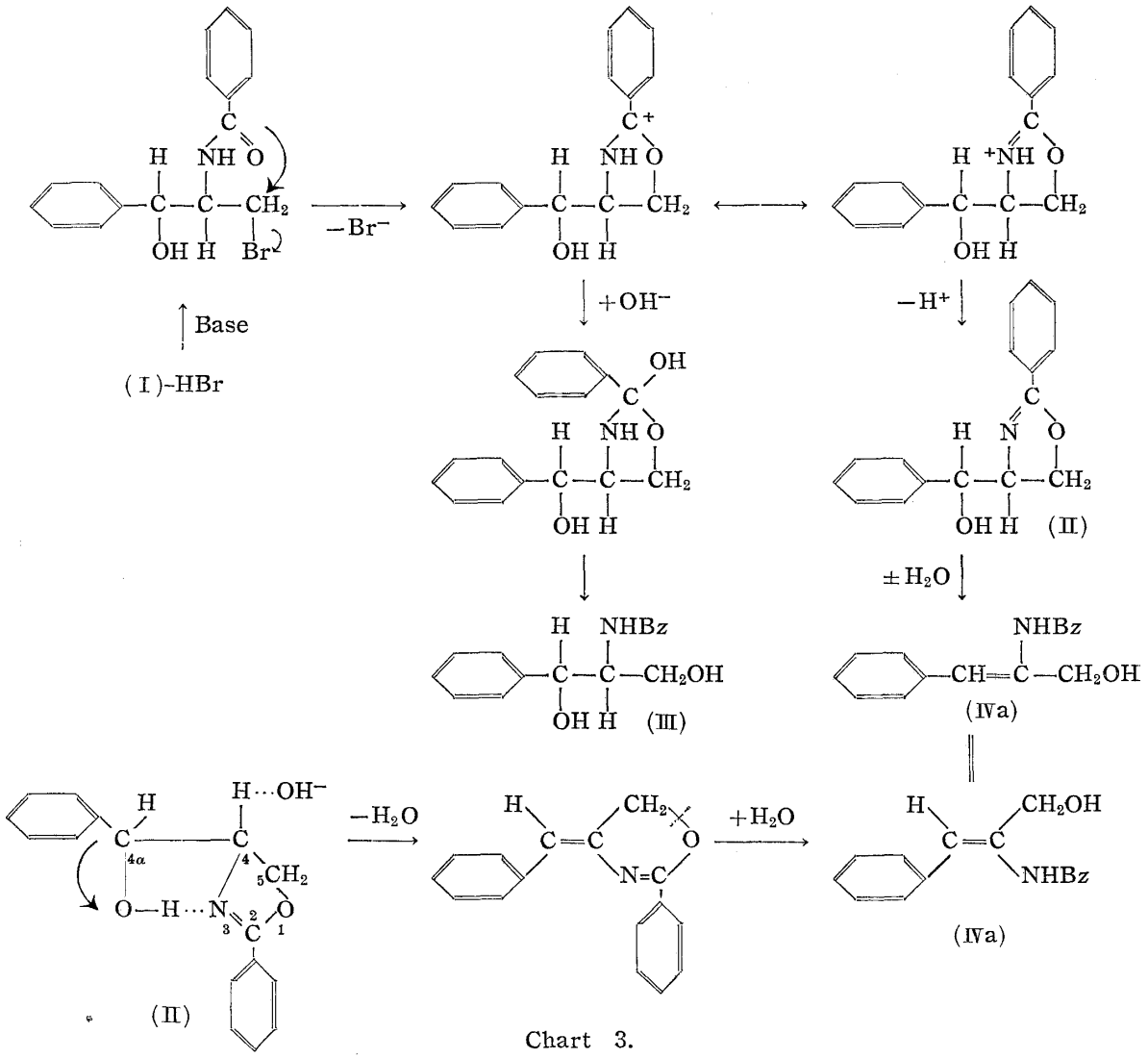

Chart 3.

boiled for 15 hrs. and concentrated *in vacuo*. The solid residue was extracted with AcOEt, washed with water, dried over anhyd. Na_2SO_4, and concentrated to give a solid, m.p. 135~150°; wt., 460 mg. Recrystallization from AcOEt gave colorless needles, m.p. 163~165°, alone and on admixture with an authentic sample of *dl-threo*-1-phenyl-2-benzoylaminopropane-1,3-diol[1]; yield, 190 mg. *Anal.* Calcd. for $C_{16}H_{17}O_3N$ (III): C, 70.83; H, 6.32; N, 5.16. Found: C, 71.13; H, 6.48; N, 5.41.

On concentration of the AcOEt mother liquor, silky needles were obtained and melted at 158~160° after recrystallization from benzene; yield, 150 mg. It did not depress the m.p. of a sample of (IV).[1] *Anal.* Calcd. for $C_{16}H_{15}O_2N$(IV): C, 75.87; H, 5.97; N, 5.53; mol. wt., 253. Found: C, 76.30; H, 6.08; N, 5.55; mol. wt. (Rast), 262. U.V. λ_{max}^{MeOH}: 240, 246 mμ (log ε 4.13, 4.12). I.R. $\lambda_{max}^{Hexachlorobutadiene}$: 3.15 (-OH), 6.07 (-C=N-), 6.23, 6.68 μ ($-C_6H_5$).

2) With anhyd. Na_2CO_3 in dehyd. EtOH: A solution of 4 g. of (I)-HBr and 4 g. of anhyd. Na_2CO_3 in 70 cc. of dehyd. EtOH was boiled for 8.5 hrs. and concentrated *in vacuo*. The oily residue was extracted with ether and the ether solution was concentrated to give a solid. Recrystallization from ether gave colorless silky needles, m.p. 159~160°, alone and on admixture with a sample of (IV); yield, 200 mg. *Anal.* Calcd. for $C_{16}H_{15}O_2N$ (IV): N, 5.53. Found: N, 5.52.

3) With NaOH in 90% MeOH: A solution of 2 g. of (I)-HBr in a mixture of 5 cc. of 10% NaOH and 45 cc. of MeOH was boiled for 3 hrs. and concentrated *in vacuo*. The solid residue was washed with water and dried, m.p. 112~130°; wt., 740 mg. Recrystallization from ether gave colorless needles, m.p. 158~160°, alone and on admixture with a sample of (IV); yield, 150 mg.

To the ethereal mother liquor, saturated ether solution of picric acid was added and yellow needles precipitated. After recrystallization from dehyd. EtOH, it melted at 139~141°, alone and on admixture with an authentic sample of (II)-picrate[1]; yield, 520 mg. *Anal.* Calcd. for $C_{22}H_{18}O_9N_4$ ((II)-picrate): N, 11.62. Found: N, 11.79.

b) From *dl-threo*-2-Phenyl-4-phenylhydroxymethyl-Δ^2-oxazoline (II). 1) With AcOK in 90% EtOH : A solution of 100 mg. of (II) and 200 mg. of anhyd. AcOK in 10 cc. of 90% EtOH was boiled for 15.5 hrs. and concentrated *in vacuo*. Ether extract of the solid residue was concentrated and colorless needles precipitated. After recrystallization from ether it melted at 158~160°, alone and on admixture with a sample of (IV); yield, 50 mg.

Further concentration of the ethereal mother liquor gave a solid, m.p. 137~147°; wt., 10 mg. It was assumed to be a mixture of (II) and (IV), but further purification was not successful.

2) With NaOH in 90% MeOH : A solution of 100 mg. of (II) in a mixture of 0.25 cc. of 10% NaOH and 2.25 cc. of MeOH was boiled for 20 hrs. and concentrated *in vacuo*. Ether extract of the solid residue was concentrated to give colorless needles. After recrystallization from ether, it melted at 158°, alone and on admixture with a sample of (IV); yield, 90 mg.

When the reaction mixture was heated for only 10 hrs., yield of (IV) was reduced to one-half.

3) Heating in 90% EtOH : A solution of 50 mg. of (II) in 5 cc. of 90% EtOH was boiled for 15 hrs. and concentrated to give a solid residue, m.p. 114~154°, which recrystallized from ether to colorless needles, m.p. 159~161°, alone and on admixture with a sample of (IV); yield, 20 mg.

From the ethereal mother liquor, a further crop of crude (IV) was obtained; wt., 10 mg.

4) Heating in 90% EtOH under Pressure : A solution of 100 mg. of (II) in 2 cc. of 90% EtOH was heated in a sealed tube at 130~140° for 12 hrs. and concentrated to give a solid residue, m.p. 123~140°; wt., 90 mg. After treatment of the solid with 10% HCl, undissolved substance was filtered off and the filtrate was made alkaline with conc. K_2CO_3 to give colorless needles. After recrystallization from ether it melted at 159~161°, alone and on admixture with a sample of (IV); yield, 30 mg.

The solid insoluble in 10% HCl was recrystallized from AcOEt to colorless needles, m.p. 163~165°, alone and on admixture with an authentic sample of (III)[1]; yield, 10 mg.[5]

c) From *dl-threo*-2-Phenyl-4-phenylacetoxymethyl-Δ^2-oxazoline (VII)[4] : A solution of 100 mg. of (VII) and 200 mg. of anhyd. AcOK in 10 cc. of 90% EtOH was boiled for 20 hrs. and concentrated *in vacuo*. The solid residue was washed with water and dried to a solid of m.p. 120~135°, which could not be purified by recrystallization. After treatment with HCl, then K_2CO_3, recrystallization from benzene gave colorless needles, m.p. 159~160°, which showed no depression with a sample of (IV); yield, 35 mg.

***dl*-1-Phenyl-2-benzoylaminopropan-3-ol (V)**—a) From *dl*-1-Phenyl-2-aminopropan-3-ol (VI) Hydrochloride[2] : 290 mg. of (VI)-HCl was benzoylated with 220 mg. (1 mole per mole of (VI)-HCl) of BzCl by the Schotten-Baumann method. Recrystallization from AcOEt gave colorless prisms, m.p. 147~149°; yield, 290 mg. *Anal.* Calcd. for $C_{16}H_{17}O_2N$ (V) : C, 75.27; H, 6.71; N, 5.49. Found : C, 75.21; H, 6.52; N, 5.19.

b) From (IV) : A solution of 100 mg. of (IV) in 15 cc. of dehyd. EtOH was hydrogenated at atmospheric pressure using 50 mg. of 10% Pd-C as a catalyst, and 12.4 cc. of H_2 was absorbed at 16°. The filtrate was concentrated to give a solid residue which recrystallized from AcOEt to colorless prisms, m.p. 148~150°, alone and on admixture with a sample of (V) derived from (VI)-HCl; yield, 90 mg. *Anal.* Calcd. for $C_{16}H_{17}O_2N$ (V) : C, 75.27; H, 6.71; N, 5.49. Found : C, 75.49; H, 6.59; N, 5.69. U.V. λ_{max}^{MeOH} mμ (log ε) : 224, 246, 249, 252 (4.05, 3.75, 3.67, 3.56). I.R. λ_{max}^{Nujol} μ : 3.01 (-NH-); 6.08, 6.45 (Amide I, II); 6.23, 6.32, 6.69 ($-C_6H_5$).

Summary

The treatment of *dl-threo*-1-phenyl-1-benzoyloxy-2-amino-3-bromopropane (I) hydrobromide in basic media yielded *dl*-1-phenyl-2-benzoylaminoprop-1-en-3-ol (or *dl*-1-phenyl-2-benzoyliminopropan-3-ol) (IV) via *dl-threo*-2-phenyl-4-phenylhydroxymethyl-Δ^2-oxazoline (II). *dl-threo*-1-Phenyl-2-benzoylaminopropane-1,3-diol (III) was also formed by treatment of hydrobromide of (I) with potassium acetate and hydrous ethanol. These formation mechanisms were discussed on the ground of stereochemical findings.

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5) The formation mechanism will be reported in future.