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22. Tanezo Taguchi and Masaharu Kojima: The Formation and Chemical Properties of Diastereomeric 1,2-Dimethyl-3-phenylaziridine.[1]

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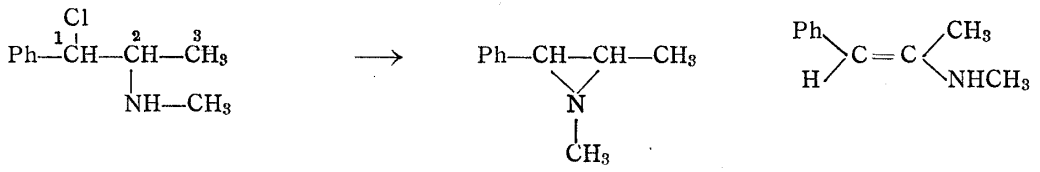
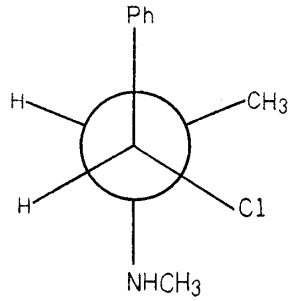
It has been reported by a few authors[2~5] that L-*erythro*-1,2-dimethyl-3-phenylaziridine (*erythro*-III) was obtained by action of NaOH on L-*threo*-1-chloro-1-phenyl-2-methylaminopropane (*threo*-II) derived from L-ephedrine (*erythro*-I), but the analogous treatment of the L-*erythro*-diastereomer (*erythro*-II) gave rather a polymerization product than the expected aziridine derivative (*threo*-III).

The failure of gaining the aziridine (*threo*-III) in the latter case had been due to the preference of elimination over internal substitution (the aziridine formation) by the con-



threo-II *erythro*-III IV

formational requirement of (*erythro*-II). Particularly Murakami and Fukumoto[5] had presumably claimed that the polymerization occurred via a supposed β-methylstyrene derivative (IV), which would result from elimination favored in the preferred conformation (*erythro*-II_A). To ascertain whether this is the case or not, the formation reaction of L-*threo*-1,2-dimethyl-3-phenylaziridine (*threo*-III) was undertaken and placed into stereochemical considerations in this paper. Approaches to the preparation of (*threo*-III) were successfully persued by two ways; one is the treatment of sulfuric ester (*threo*-V) of L-ψ-ephedrine (*threo*-I) with alkali hydroxide and the other the analogous treatment of (*erythro*-II) in an improved practice where cares were paid to prevent polymerization.



erythro-(II_A)

Schmidt[6] has reported that the sulfuric ester (*threo*-V) was solely obtained by action of conc. sulfuric acid either on L-ephedrine (*erythro*-I) with inversion or on L-ψ-ephedrine (*threo*-I) with retention.

Takamatsu[7] used 85% sulfuric acid for the same esterification where the resulting ester was immediately converted to phenylacetone by heating in water without isolation, though the configuration of the ester was presumably assigned as L-*threo* form (*threo*-V). Since the ester had been obtained in liquid state, its characterization was indirectly carried out on the basis of chemical and physical properties. The present authors tried the esterification of L-ephedrine (*erythro*-I) and L-ψ-ephedrine (*threo*-I) by the adaptation of Dicky's procedure[8] using chlorosulfonic acid. After the reaction was repeated three times

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1) Studies in stereochemistry. XXII.
2) S. Ikuma: Yakugaku Zasshi, **72**, 951(1952).
3) K. Tanaka, T. Sugawa: *Ibid.*, **72**, 1548(1952).
4) M. Murakami, T. Fukumoto: Nippon Kagaku Zasshi, **76**, 270(1955).
5) K. Tanaka: Yakugaku Zasshi, **70**, 212, 216, 220 (1950).
6) E. Schmidt: Arch. Pharm., **252**, 89(1914).
7) S. Takamatsu: Yakugaku Zasshi, **76**, 1244(1956).
8) F. H. Dicky, W. Ficket, H. J. Lucas: J. Am. Chem. Soc., **74**, 944(1952).

samples of the ester from each run and each of the two starting materials (*erythro*- and *threo*-I) gave equally phenylacetone by heating in water and showed $[\alpha]_D$ +2~+7° (EtOH), indicating analogy with the findings by the former authors.[6,7] Therefore the esters derived from (*erythro*-I) and (*threo*-I) were supposed to be identical and tentatively assigned L-*threo* form in the adaptation of the previous assignment.[6,7] The supposed L-*threo* ester (*threo*-V) was carefully added to an aqueous NaOH solution below 0° and distilled by steam. The distillate containing oily layer was extracted with ether and washed with 0.1*N* HCl. From the ether layer, phenylacetone was isolated as a semicarbazone.

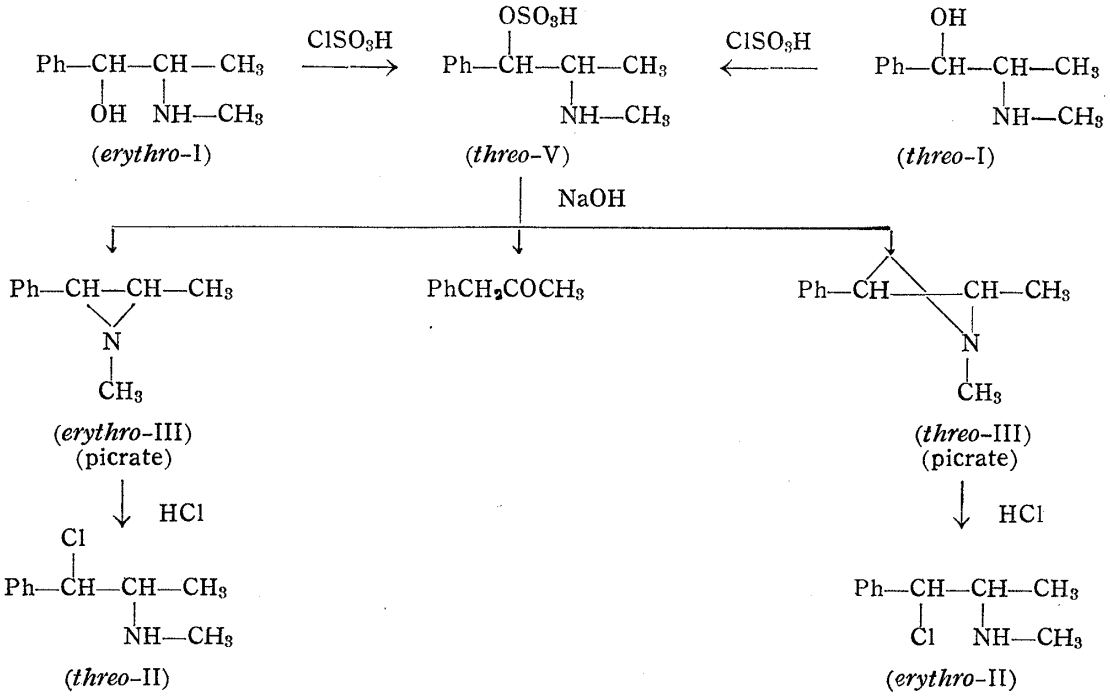


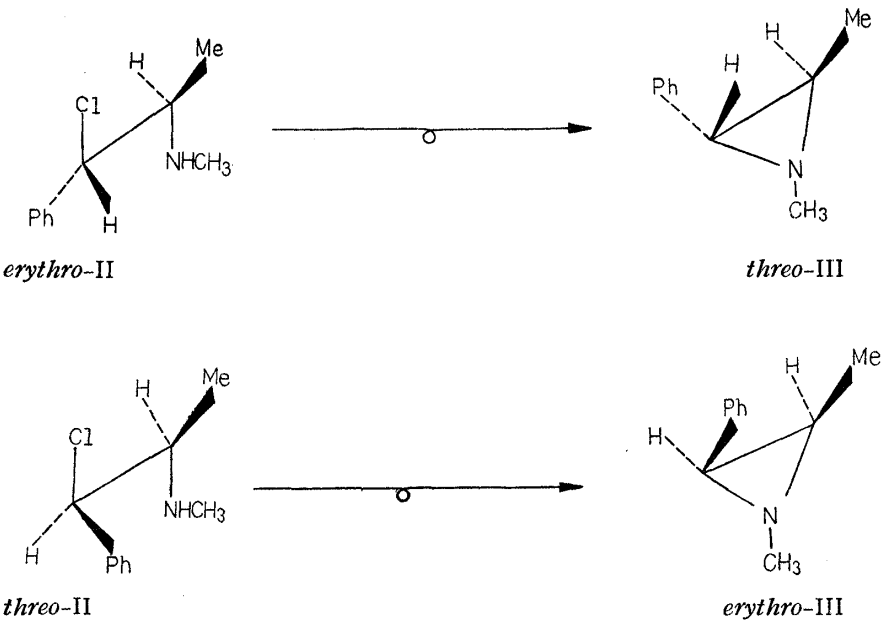
Chart 1.

The HCl solution was made alkaline and extracted again with ether. The ethereal solution gave two kinds of picrate, m.p. 83~85° and 131~132°. The former picrate was identical with the known (*erythro*-III·picrate) and the latter one was identified as (*threo*-III·picrate) on the basis of elemental microanalyses and the fact that it gave (*erythro*-II·HCl) ($[\alpha]_D^{24}$ +100°, EtOH) by action of alcoholic HCl in contrast with the formation of (*threo*-II·HCl) ($[\alpha]_D^{25}$ −65°, EtOH) on the same treatment of (*erythro*-III·picrate).

The mixed aziridines (III, $[\alpha]_D^{25}$ −45°, benzene) before their separation by derivation to their picrate gave a mixture of (*erythro*-II·HCl) and (*threo*-II·HCl) on treatment with alcoholic HCl, which showed $[\alpha]_D^{23}$ +7° (EtOH). Calculating from optical rotation of the mixture ($[\alpha]_D^{23}$ +7°) and the pure compounds ($[\alpha]_D^{24}$ +100° and −65°, EtOH), the formation ratio of (*erythro*-II·HCl) and (*threo*-II·HCl) was 57 : 43 and it also corresponds roughly to the formation ratio of the aziridines (*threo*- and *erythro*-III), showing the predominance of (*threo*-III) over (*erythro*-III). When the mixture of the free aziridines (III) was allowed to stand in air or in solution, it became turbid and finally deposited a gummy substance. Thus it was so easy to polymerize that it was impossible to isolate (*threo*-III) as free base from the mixture. Attention may be focused also on the stereochemical result that (*erythro*- and *threo*-III) were simultaneously formed from (*threo*-V). However, it is not right to attribute the result to any reason, because the configuration of the starting material has not been completely decided. Since, as above-stated, the attempted formation of (*threo*-III) by the treatment of (*erythro*-II) with alkali hydroxide had been unsuccessful,[4,5] the alter-

native approach to acquirement of (*threo*-III) from (*erythro*-II) was carried out in an improved procedure as follows: An aqueous solution of NaOH was added, while shaking, to an aqueous solution of (*erythro*-II) covered with ether at room temperature. After further shaking for a few minutes, the ether layer was separated, evaporated to dryness, and immediately treated with a saturated ethereal solution of picric acid to give a picrate which, after rapid recrystallization from benzene, was identical with (*threo*-III·picrate) derived from the *threo*-sulfate (*threo*-V). The free *threo*-aziridine (*threo*-III) became turbid and finally solidified on allowing to stand in air, suggesting that it easily polymerizes. Though it has been often claimed that the treatment of (*erythro*-II) with alkali hydroxide initially gave the supposed β-methylstyrene derivative or others which might suffer polymerization,[4,5] it seems more probable that the polymerization occurred via the *threo*-aziridine (*threo*-III) in the light of the experimental facts obtained here.

Moreover, it is concluded that the formation of the *threo*-aziridine (*threo*-III) is easier than that of the *erythro*-aziridine (*erythro*-III) from the observation that the formation ratio was approximately 57:43 and also from the theoretical consideration that the steric interaction of phenyl and methyl groups in the transition state of the formation reaction is stronger in (*erythro*-III) than in (*threo*-III) as shown in Chart 2. The theoretical consideration is



erythro-II *threo*-III

threo-II *erythro*-III

Chart 2.

supported by the accepted generalization[9] that 1,2-*trans*-cyclization reaction occurs more rapidly in the diastereomer where the large groups are not eclipsed. Curtin,[10] in particular, has emphasised the role of such a *cis*-effect in controlling the relative rate of 1,2-*trans*-cyclization reactions. The only reason why (*threo*-III) had not been isolated is that it polymerized easier, and not that it was not formed in the reactions discussed here.

The authors are indebted to Messrs. K. Funakoshi and T. Horai for elemental microanalyses.

Experimental

L(−)-*erythro*-1-Chloro-1-phenyl-2-methylaminopropane (*erythro*-II)·HCl—Prepared by Tanaka's procedure,[5] m.p. 197~198° (decomp.), $[\alpha]_D^{24}$ -65.5° (EtOH). (Tanaka: m.p. 198° (decomp.), $[\alpha]_D^{11}$ -65°, EtOH).

9) D. H. R. Barton, R. C. Cookson: Quart. Revs. (London), **10**, 54 (1956).
10) D. Y. Curtin: Record Chem. Progr. (Kresge-Hooker Sci. Lib.), **15**, 111 (1954).

L(+)-***threo*-1-Chloro-1-phenyl-2-methylaminopropane (*threo*-II)·HCl**—Prepared by Tanaka's procedure,[5] m.p. 200~201°, $[\alpha]_D^{24}$ +100.7° (EtOH). (Tanaka: m.p. 202°, $[\alpha]_D^{10}$ +114°, EtOH).

L(−)-***erythro*-1,2-Dimethyl-3-phenylaziridine (*erythro*-III)**—Prepared by Tanaka's procedure,[5] $[\alpha]_D^{22}$ −144.4° (benzene). (Tanaka: $[\alpha]_D^{11}$ −127°, EtOH). Picrate: Yellow needles (from acetone-ether), m.p. 83~85°. *Anal.* Calcd. for $C_{16}H_{16}O_6N_4$: C, 51.04; H, 4.29; N, 14.89. Found: C, 51.00; H, 4.34; N, 14.80.

The Supposed L(+)-ψ-Ephedrine O-Sulfate (*threo*-V)—a) To 1 mole of L(−)-ephedrine (*erythro*-I) was added 1 mole. of chlorosulfonic acid and the mixture was warmed on a boiling water bath for 40 mins. After replacing the water bath by an oil bath, heating was continued for 1.5 hrs. under reduced pressure by water jet pump controlling temperature at 150°. The whole treatment was carried out avoiding moisture. The reaction mass did not crystallize and remained vitreous. The optical rotation of three runs was measured after 30 min. since dissolved and showed $[\alpha]_D^{20}$ +4.5° (EtOH); $[\alpha]_D^{20}$ +1.9° (EtOH) and $[\alpha]_D^{21}$ +6.6° (EtOH).

b) L(+)-ψ-Ephedrine (*threo*-I) was treated exactly as in a) and gave rise to the analogous result. The optical rotatory powers of three runs (measured after 30 mins. since dissolved): $[\alpha]_D^{22}$ +7.2° (EtOH); $[\alpha]_D^{20}$ +2.3° (EtOH); $[\alpha]_D^{21}$ +6.9° (EtOH).

Hydrolysis of the supposed (*threo*-V). The Formation of Phenylacetone—a) Two g. of the supposed (*threo*-V) derived from L(−)-ephedrine in 5 cc. of water was heated on a water bath to become immediately turbid and then deposit an oily substance. After 30 mins.' heating, the mixture was extracted with ether and evaporated to dryness, $b.p_{14}$ 97~100°; yield, 0.51 g. Semicarbazone: Recrystallized from EtOH, m.p. 191~192°, alone and on admixture with an authentic sample of phenylacetone semicarbazone. *Anal.* Calcd. for $C_{10}H_{13}ON_3$: C, 62.79; H, 6.85; N, 21.98. Found: C, 62.94; H, 6.85; N, 21.71.

b) The supposed (*threo*-V) was hydrolysed on allowing to stand at room temperature to give the same product as in a).

c) The supposed (*threo*-V) derived from L(+)-ψ-ephedrine was treated exactly as in a) and b) to gain the analogous results.

Treatment of the supposed (*threo*-V) with KOH accompanied by HCl. The Formation of a Mixture of L(−)-*erythro*-1-Chloro-1-phenyl-2-methylaminopropane (*erythro*-II) and the L(+)-*threo*-Diastereomer (*threo*-II).—a) To the supposed (*threo*-V) prepared by action of 3.9 g. of chlorosulfonic acid on 5 g. of (*erythro*-V) dissolved in 11 cc. of water was added 6.7 g. of KOH dissolved in 6.8 cc. of water and the mixture was heated on a boiling water bath for 30 mins. To the mixture was added 10 cc. of water and submitted to steam-distillation. The distillate was extracted with ether and the ether layer was washed in series with 110 cc. of 0.1*N* HCl in total. From the ethereal layer 1.18 g. of phenylacetone was isolated as semicarbazone, m.p. 191~192°. The HCl solution was made alkaline with 20% NaOH, extracted with ether, dried over KOH, and freed of solvent to leave 1.79 g. of a basic oil, $b.p_{25}$ 80~93°, $[\alpha]_D^{22}$ −45.1° (benzene). After rapid distillation, 2 g. of the distillate was immediately dissolved in 1 cc. of 10% ethanolic HCl, boiled on a water bath for 5 mins., and evaporated to dryness. On addition of ether the residue crystallized, m.p. 181~186°, $[\alpha]_D^{23}$ +7.2° (EtOH), and showed no depression of m.p. on admixture with either (*threo*-II·HCl) or (*erythro*-II·HCl). When the basic oil was dissolved in EtOH without treatment of HCl, it became turbid on allowing to stand.

b) Also when the supposed (*threo*-V) derived from L(+)-ψ-ephedrine was treated as in a), it showed the result analogous with a).

Treatment of the supposed (*threo*-V) with KOH accompanied by Picric Acid. The simultaneous Formation of (*threo*-III) and (*erythro*-III) Picrate.—One g. of the basic oil, obtained on treatment of the supposed (*threo*-V) with KOH just as the preceding description, was immediately dissolved in a small amount of ether and 80 cc. of 1% ethereal picric acid solution added to precipitate a picrate, m.p. 130~131°; yield, 1 g., which, after filtration, was rapidly recrystallized[11] from benzene to give yellow prisms, m.p. 131~132°. *Anal.* Calcd. for $C_{16}H_{16}O_6N_4$ (*threo*-III·picrate): C, 51.04; H, 4.29 N, 14.89. Found: C, 51.02; H, 4.11; N, 15.20. To the mother liquor was again added 36 cc. of 1% ethereal picric acid solution to precipitate a gummy picrate which crystallized while scratching, m.p. 82~83°; yield, 0.65 g. Recrystallization from acetone-ether gave yellow needles, m.p. 83~85°, which were identified as (*erythro*-III·picrate) by a mixed m.p. determination.

Derivation of (*threo*-III·Picrate) to (*erythro*-II·HCl) with Inversion—Two hundred mg. of (*threo*-III·picrate) was dissolved in 2 cc. of 10% ethanolic HCl, heated on a water bath for 10 mins., freed of EtOH, and washed with ether many times till picric acid had been completely removed, m.p. 197°; yield, 0.09 g. Recrystallization from EtOH gave colorless plates, m.p. 197~198°, $[\alpha]_D^{25}$ −65.5° (EtOH), which showed no depression of m.p. on admixture with (*erythro*-II·HCl).[12]

11) Recrystallization succeeded only in use of benzene and rapid treatment.
12) An attempt to derive the picrate to the free base was unsuccessful because of polymerization.

Derivation of (*erythro*-III·Picrate) to (*threo*-II·HCl) with Inversion—(*erythro*-III·Picrate) was treated exactly as (*threo*-III·picrate) to give (*threo*-II·HCl) whose identification was persued by a mixed m.p. determination, m.p. 199~200°, $[\alpha]_D^{24}$ +99.7° (EtOH).

The Formation of (*threo*-III·Picrate) from (*erythro*-II·HCl)—To 0.2 g. of (*erythro*-II·HCl) dissolved in 3 cc. of water was added 3 cc. of ether and then 3 cc. of 10% NaOH, and the mixture was shaken exactly for 5 mins. The aqueous layer was washed with 2 cc. of water and evaporated to dryness. To the remaining oil was added a saturated ethereal solution of picric acid to deposit yellow crystals. The yellow crystals were dissolved in 2 cc. of acetone and after filtering the undissolved substance,[13] evaporated to dryness, m.p. 130~132°; yield, 0.13 g. Rapid recrystallization from benzene gave yellow prisms, m.p. 131~132°, which were identical with (*threo*-III·picrate) derived from the supposed (*threo*-V) by a mixed m.p. determination. On treatment of ethanolic HCl the picrate gave (*erythro*-II·HCl), m.p. 197°. The ethereal oil before the treatment of picric acid was comparatively stable in ether, but evaporation of ether made the oil turbid and finally solid, suggesting change into a polymerization product, m.p. 270°.

Summary

L-*threo*-1,2-Dimethyl-3-phenylaziridine (*threo*-III) was, for the first time, isolated in the form of picrate either partly by action of KOH on the supposed L(+)-ψ-ephedrine O-sulfate (*threo*-V) or wholly by action of NaOH on L(+)-*threo*-1-chloro-1-phenyl-2-methylamino-propane (*threo*-II). These observations revised the previous claim that the reaction in the latter case would not initially pass into the aziridine, but into others, e.g. β-methylstyrene derivative, which could not be identified because it polymerized rapidly. The aziridine polymerizes very easily in the free state and more or less easily even in the salt form. It was also discussed that the steric requirement for the aziridine formation favored L-*threo*-aziridine more than the L-*erythro*-diastereomer in the transition state of the reaction. The conclusion was supported by the formation ratio of both aziridines roughly calculated on the ground of optical rotatory power.

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13) It was an amorphous substance which did not dissolve in organic solvents and accordingly seemed to be the picrate of polymer of the aziridine.