Two DL-isomers of 1-(*p*-nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediol (I), the position isomers of chloramphenicol, were derived from ⅩⅢ.

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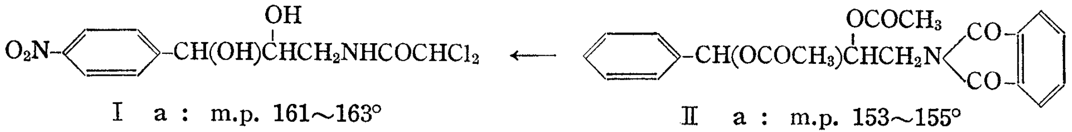
76. **Atsusuke Terada, Hiroo Itō, and Masatoshi Nagawa** : Determination of Configurations of the Two DL-Isomers of 1-(*p*-Nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediols.[*1]

(*Central Research Laboratories, Sankyo Co., Ltd.*[*2])

In the preceding paper1) the authors reported that two DL-isomers of 1-(*p*-nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediols (I), which are related to chloramphenicol in position isomerism, were obtained as two sorts of crystals showing m.p. 161∼163° (Ia) and m.p. 151∼153° (Ib). In the present paper, configurations of these isomers were determined.



I a : m.p. 161∼163°
b : m.p. 151∼153°

Ⅱ a : m.p. 153∼155°
b : m.p. 175°

As reported in the preceding paper1), Ia and Ib were derived from the corresponding 1-phenyl-3-phthalimido-1,2-propanediol diacetates (Ⅱa and Ⅱb) as products of m.p. 153∼155° (Ⅱa) and m.p. 175° (Ⅱb) respectively, without any change in the configuration. Therefore, if the configurations of the two isomers of Ⅱ are determined, the configurations of the two isomers of I can be elucidated. In order to determine the configurations of Ⅱa and Ⅱb, the following method was employed, which was diagramatically shown in Chart 1.

Cinnamyl chloride (Ⅳ) was obtained by chlorination of *trans*-cinnamyl alcohol (Ⅲ) according to the method of Gilman.2) Treatment of Ⅳ with potassium phthalimide according to the procedure of Gensler3) gave N-cinnamylphthalimide (Ⅴ). Oxidation of Ⅴ with potassium permanganate yielded 1-phenyl-3-phthalimido-1,2-propanediol (Ⅵa), m.p. 122°. Ⅵa may be considered to be a *threo* compound, because a double bond can be hydroxylated in *cis* fashion with potassium permanganate and after the oxidation a *trans* olefin affords a *threo* compound. On the other hand, Ⅴ was oxidized with perbenzoic acid, giving epoxide (Ⅶ).

Hydrolysis of Ⅶ yielded 1-phenyl-3-phthalimido-1,2-propanediol (Ⅵb), m.p. 142°. Ⅵb may be considered to be an *erythro* compound, because the epoxide obtained from *trans*-Ⅴ may be opened in *trans* manner and thus the geometry permits the formation

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[*2] Hiromachi, Shinagawa-ku, Tokyo (寺田敦祐, 伊藤博雄, 名川方敏).

1) A. Terada, H. Itō, M. Nagawa : This Bulletin, **14**, 528 (1966).

2) H. Gilman, S. Harris : Rec. Trav. Chim., **50**, 1052 (1931).

3) W. Gensler, J. Rocket : J. Am. Chem. Soc., **77**, 3262 (1955).

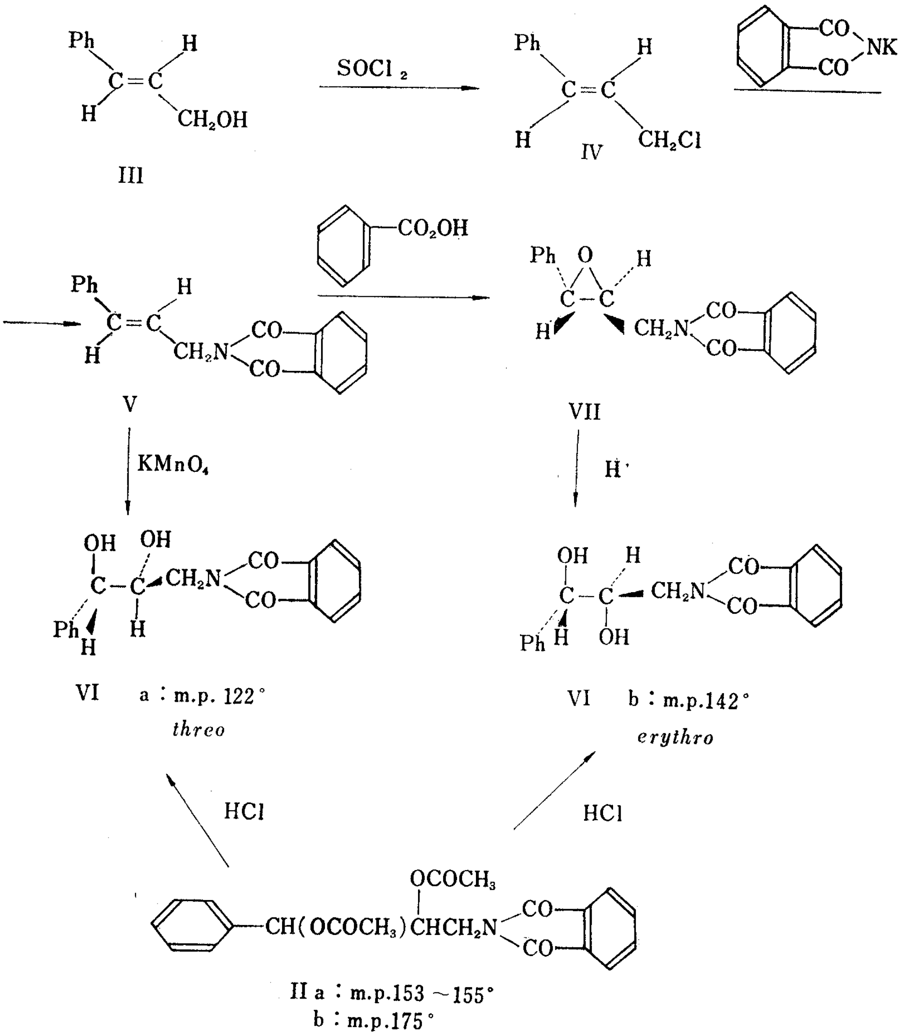


Chart 1.

of the *erythro* isomer.

To correlate Ⅱa and Ⅱb to Ⅵ, they were hydrolyzed with diluted hydrochloric acid, giving two kinds of crystals of m.p. 122° (from Ⅱa) and m.p. 142° (from Ⅱb). The former was identical with Ⅵa and the latter with Ⅵb. Thus, it is supported by the findings to assign the configuration of Ⅱa as a *threo* form and Ⅱb as an *erythro* form.

Furthermore, to confirm the configurational assignment of Ⅵa and Ⅵb, the method was employed as shown in Chart 2.

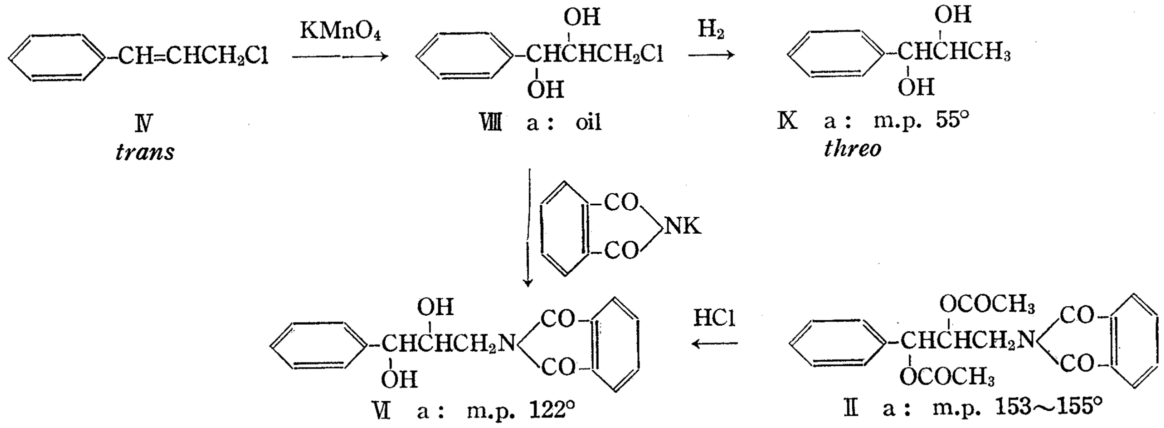


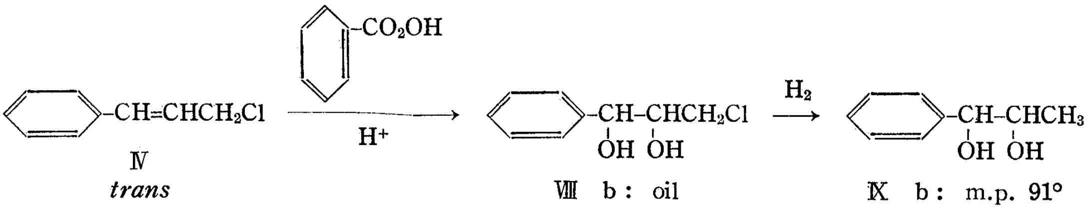
Chart 2.

Oxidation of IV with potassium permanganate gave 1-phenyl-3-chloro-1,2-propanediol (VIIIa). Catalytic hydrogenation of VIIIa over palladium on charcoal afforded 1-phenyl-1,2-propanediol, m.p. 55°, which was identical with IXa (*threo*) synthesized according to the method of Fischer,[4] Witkop.[5] Then VIIIa was reacted with potassium phthalimide, yielding 1-phenyl-3-phthalimido-1,2-propanediol (VI), m.p. 122°, which was identical to VIa obtained from hydrolysis of IIa with diluted hydrochloric acid.

This suggests that VIa is a *threo* compound and accordingly IIa is a *threo* compound.

On the other hand, IV was oxidized with perbenzoic acid, giving 1-phenyl-3-chloropropanediol (VIIIb). Catalytic reduction of VIIIb with palladium on charcoal yielded 1-phenyl-1,2-propanediol (IX), m.p. 91°, which was identical with IXb synthesized according to the method of Witkop[5].

As IXb has been proved to be an *erythro* compound by Fischer and Witkop, VIIIb might be an *erythro* compound. However, VIIIb was not reacted with potassium phthalimide. But, it supports the assignment of VIb and IIb as an *erythro* form that VIb and IIb were not identical with VIa and IIa.



Accordingly configurations of Ia and Ib were established. Moreover, it was proven that the stereochemical assumption for the oxidation of V with permanganate and perbenzoic acid was sound.

Experimental*3

DL-*threo*-1-Phenyl-3-phthalimido-1,2-propanediol (VIa). **i) Oxidation of V with Potassium Permanganate**——V[3] (3.8 g.) was dissolved in purified acetone (200 ml.) and mixed with the solution of $KMnO_4$ (2.2 g.) and H_2O (200 ml.) at 0~5°. $MgSO_4$ (4 g.) was added to the mixture and stirred for 6 hr. at 0°. After filtration, the filtrate was concentrated to 100 ml. under reduced pressure and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a crystalline residue. The residue was dissolved in benzene and submitted to silica gel chromatography. Elution with benzene gave VIa (1.5 g.), as colorless crystals of m.p. 122°. *Anal.* Calcd. for $C_{17}H_{15}O_4N$: C, 68.68; H, 5.55; N, 4.71. Found : C, 68.67; H, 5.08; N, 4.77.

ii) Hydrolysis of IIa——A mixture of IIa[1] (2 g.), MeOH (60 ml.), and HCl (6 ml.) was heated for 1 hr. on a boiling water bath. After evaporating MeOH, a small amount of water was added and the mixture was extracted with AcOEt. The organic layer was washed with H_2O, satd. $NaHCO_3$ solution, dried and evaporated to give crystals of m.p. 95~105° (1.5 g.), which were recrystallized from benzene to yield VIa, as colorless crystals, m.p. 122°. The crystals were identical to those obtained at i).

iii) Reacting VIIIa with Potassium Phthalimide——VIIIa (an oil) (2 g.), potassium phthalimide (2.6 g.), and $HCON(CH_3)_2$ (10 ml.) were heated for 4 hr. at 80°. After cooling, the mixture was filtered and dil. HCl was added to the filtrate. The mixture was extracted with AcOEt and the extract was washed with dil. KOH solution, H_2O, dried and evaporated to give colorless crystals. Recrystallization from benzene afforded VIa (0.25 g.), m.p. 122°. *Anal.* Calcd. for $C_{17}H_{15}O_4N$: C, 68.68; H, 5.55; N, 4.71. Found : C, 68.79; H, 5.30; N, 4.58.

DL-*erythro*-1-Phenyl-3-phthalimido-1,2-propanediol (VIb). **i) Oxidation of V with Perbenzoic Acid**——V (8 g.) in $CHCl_3$ (60 ml.) was added to the solution of perbenzoic acid (10 g.) (obtained from benzoyl peroxide 25 g. in the usual manner) in $CHCl_3$ (100 ml.) at −10°. After stirring for 1 hr. at 0°, the solution was allowed to stand for 2 days in refrigerator. The solution was washed with 5% $FeSO_4$ solution, dil. NaOH solution, H_2O, dried and evaporated to give colorless crystals, which were recrystallized from MeOH to yield VII (0.9

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*3 All melting points are uncorrected.

4) F. Fischer : Ber., **89**, 2438 (1956).

5) B. Witkop, C. Foltz : J. Am. Chem. Soc., **79**, 197 (1957).

g.), m.p. 108～110°. The crystals were dissolved in AcOEt (40 ml.) and stirred with 2*N* H_2SO_4 (44 ml.) for 24 hr. at room temperature. The solution was extracted with AcOEt and the organic layer was washed with satd. $NaHCO_3$ solution, H_2O, dried and evaporated. Ether was added to the residue to give a crystalline residue, which was washed with MeOH and then recrystallized from MeOH to afford Ⅶb, as crystals, m.p. 142°. *Anal.* Calcd. for $C_{17}H_{15}O_4N$: C, 68.68; H, 5.55; N, 4.71. Found : C, 68.63; H, 5.38; N, 4.60.

ii) **Hydrolysis of IIb**——A mixture of Ⅱb[1] (5 g.), MeOH (150 ml.) and conc. HCl (15 ml.) was refluxed for 1 hr. Evaporating MeOH afforded an oily residue which crystallized gradually. Recrystallization from MeOH gave crystals (3.1 g.), m.p. 141～142°. The crystals were identical with those obtained in i).

DL-***threo*-1-Phenyl-1,2-propanediol (IXa)**——Cinnamyl chloride (Ⅳ)[2] (20 g.) was dissolved in EtOH (200 ml.) and $MgSO_4$ (21 g.) was added. To the mixture, a solution of $KMnO_4$ (25 g.) in H_2O (600 ml.) was added during 1 hr. at −40～−30°. After removing precipitating MnO_2 by filtration, the filtrate was evaporated and the residue was extracted with ether. The extract was dried with Na_2SO_4 and evaporated to afford an oil (12.5 g.) (Ⅷa). The oil was dissolved in MeOH (150 ml.) and shaken with Pd-C prepared from 0.5% $PdCl_2$ (200 ml.) and charcoal (3 g.) in an atmosphere of H_2. The catalyst was removed by filtration and the solvent was evaporated. To the residue, a small amount of H_2O was added and the mixture was extracted with ether. The extract was dried and evaporated to give an oil, which crystallized during allowing to stand in the refrigerator after adding ether and ligroin. Colorless crystals (7 g.), m.p. 55° were obtained, which were identical with Ⅸa prepared according to the procedure of Witkop[5]. *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.86. Found : C, 71.05; H, 7.85.

DL-***erythro*-1-Phenyl-1,2-propanediol (IXb)**——Ⅳ (15.2 g.) was added dropwise to a $CHCl_3$ solution of perbenzoic acid prepared from benzoyl peroxide (50 g.) at −10°. The solution was stirred for 50 hr. at 0°. The $CHCl_3$ solution was washed with $FeSO_4$ solntion, 2*N* NaOH, H_2O and dried. Evaporation of the solution gave colorless crystals, to which 2*N* H_2SO_4 (90 ml.) was added. The mixture was stirred for 40 hr. and extracted with ether. The extract was washed with satd. $NaHCO_3$ solution, H_2O, dried and evaporated to give an oil (13 g.) (Ⅷb). The oil (6 g.) was dissolved in MeOH (60 ml.) and shaken with Pd-C prepared from 0.5% $PdCl_2$ (100 ml.) and charcoal (1.4 g.) in an atmosphere of H_2. The catalyst was removed by filtration and the filtrate was evaporated. The residue was extracted with ether and the ether solution was dried. After removal of ether, the residue was distilled under a reduced pressure to give an oil (3 g.), b.p$_2$ 80°. To the oil, acetone and ligroin were added and the mixture was allowed to stand with Ⅸb prepared according to the procedure of Witkop. *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.86. Found : C, 70.90; H, 7.86.

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Summary

The configurational investigation of the two DL-isomers of 1-(*p*-nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediol which were obtained as the substances of m.p. 161～163° (Ia) and m.p. 151～153° (Ib) in the previous study[1] was persued and Ia and Ib were assigned as *threo* and *erythro* forms respectively.

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