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 Itô, and Masatoshi Nagawa : Determination of Configurations of the Two DL-Isomers of 1-(p-Nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediols.\textsuperscript{a1}

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In the preceding paper\textsuperscript{b1} 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.

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\begin{align*}
\text{I} & : \text{m.p. 161~163°} \\
\text{b} & : \text{m.p. 151~153°}
\end{align*}
\]

As reported in the preceding paper\textsuperscript{b1}, 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 diagrammatically shown in Chart 1.

Cinnamyl chloride (N) was obtained by chlorination of trans-cinnamyl alcohol (III) according to the method of Gilman.\textsuperscript{b3} Treatment of N with potassium phthalimide according to the procedure of Gensler\textsuperscript{b4} gave N-cinnamylphthalimide (V). Oxidation of V with potassium permanganate yielded 1-phenyl-3-phthalimido-1,2-propanediol (Va), m.p. 122°. Va may be considered to be a three compound, because a double bond can be hydroxylated in cis fashion with potassium permanganate and after the oxidation a trans olefin affords a three 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 (VIII), m.p. 142°. VIII 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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1) A. Terada, H. Itô, M. Nagawa : This Bulletin, 14, 528 (1966).
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 1.

Chart 2.
Oxidation of $\mathbf{V}$ with potassium permanganate gave 1-phenyl-3-chloro-1,2-propanediol (\(\mathbf{VIa}\)). Catalytic hydrogenation of \(\mathbf{VIa}\) over palladium on charcoal afforded 1-phenyl-1,2-propanediol, m.p. 55°, which was identical with \(\mathbf{V}\) \((\text{trans})\) synthesized according to the method of Fischer,\(^4\) Witkop,\(^5\) Then \(\mathbf{VIa}\) was reacted with potassium phthalimide, yielding 1-phenyl-3-phthalimido-1,2-propanediol (\(\mathbf{VI}\)), m.p. 122°, which was identical to \(\mathbf{V}\) obtained from hydrolysis of \(\mathbf{IIa}\) with diluted hydrochloric acid.

This suggests that \(\mathbf{VIa}\) is a \(\text{trans}\) compound and accordingly \(\mathbf{IIa}\) is a \(\text{trans}\) compound.

On the other hand, \(\mathbf{V}\) was oxidized with perbenzoic acid, giving 1-phenyl-3-chloro-propanediol (\(\mathbf{VIb}\)). Catalytic reduction of \(\mathbf{VIb}\) with palladium on charcoal yielded 1-phenyl-1,2-propanediol (\(\mathbf{XI}\)), m.p. 91°, which was identical with \(\mathbf{Xb}\) synthesized according to the method of Witkop\(^5\).

As \(\mathbf{XIb}\) has been proved to be an \(\text{erythro}\) compound by Fischer and Witkop, \(\mathbf{VIb}\) might be an \(\text{erythro}\) compound. However, \(\mathbf{VIb}\) was not reacted with potassium phthalimide. But, it supports the assignment of \(\mathbf{VIb}\) and \(\mathbf{XIb}\) as an \(\text{erythro}\) form that \(\mathbf{VIb}\) and \(\mathbf{XIb}\) were not identical with \(\mathbf{VIa}\) and \(\mathbf{IIa}\).

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

**Experimental**\(^3\)

**DL-\(\text{trans}\)-1-Phenyl-3-phthalimido-1,2-propanediol (\(\mathbf{VIa}\)).** i) Oxidation of \(\mathbf{V}\) with Potassium Permanganate—\(\mathbf{V}\) \((3.8\, \text{g})\) was dissolved in purified acetone \((200\, \text{ml})\) and mixed with the solution of \(\text{KMnO}_4\) \((2.5\, \text{g})\) and \(\text{H}_2\text{O}_2\) \((200\, \text{ml})\) at 0–5°. \(\text{MgSO}_4\) \((4\, \text{g})\) 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 \(\text{AcOEt}\). The extract was washed with water, dried over \(\text{Na}_2\text{SO}_4\), and evaporated to give a crystalline residue. The residue was dissolved in benzene and submitted to silica gel chromatography. Elution with benzene gave \(\mathbf{VIa}\) \((1.5\, \text{g})\), as colorless crystals of m.p. 122°. Anal. Calcd. for \(\text{C}_7\text{H}_8\text{O}_3\text{N}\): C, 68.68; H, 5.55; N, 4.71. Found: C, 68.67; H, 5.08; N, 4.77.

ii) Hydrolysis of \(\mathbf{IIa}\)—A mixture of \(\mathbf{IIa}\) \((2\, \text{g})\), \(\text{MeOH}\) \((60\, \text{ml})\), and \(\text{HCl}\) \((6\, \text{ml})\) was heated for 1 hr. on a boiling water bath. After evaporating \(\text{MeOH}\), a small amount of water was added and the mixture was extracted with \(\text{AcOEt}\). The organic layer was washed with \(\text{H}_2\text{O}\), satd. \(\text{NaHCO}_3\) solution, dried and evaporated to give crystals of m.p. 95–105° \((1.5\, \text{g})\), which were recrystallized from benzene to yield \(\mathbf{V}\) as colorless crystals, m.p. 122°. The crystals were identical to those obtained at i).

iii) Reacting \(\mathbf{VIIa}\) with Potassium Phthalimide—\(\mathbf{VIIa}\) \((an\, \text{oil})\) \((2\, \text{g})\), potassium phthalimide \((2.6\, \text{g})\), and \(\text{HCON(CH}_3)_2\) \((10\, \text{ml})\) were heated for 4 hr. at 89°. After cooling, the mixture was filtered and dil. \(\text{HCl}\) was added to the filtrate. The mixture was washed with \(\text{AcOEt}\) and the extract was washed with dil. \(\text{KOH}\) solution, \(\text{H}_2\text{O}\), dried and evaporated to give colorless crystals. Recrystallization from benzene afforded \(\mathbf{V}\) \((0.25\, \text{g})\), m.p. 122°. Anal. Calcd. for \(\text{C}_7\text{H}_8\text{O}_3\text{N}\): C, 68.68; H, 5.55; N, 4.71. Found: C, 68.79; H, 5.30; N, 4.58.

**DL-\(\text{erythro}\)-1-Phenyl-3-phthalimido-1,2-propanediol (\(\mathbf{VIb}\)).** i) Oxidation of \(\mathbf{V}\) with Perbenzoic Acid—\(\mathbf{V}\) \((8\, \text{g})\) in \(\text{CHCl}_3\) \((60\, \text{ml})\) was added to the solution of perbenzoic acid \((10\, \text{g})\) \((obtained\, \text{from\, benzoyl\, peroxide}\, 25\, \text{g.\, in\, the\, usual\, manner})\) in \(\text{CHCl}_3\) \((100\, \text{ml})\) 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, \(\text{H}_2\text{O}\), dried and evaporated to give colorless crystals, which were recrystallized from \(\text{MeOH}\) to yield \(\mathbf{V}\) \((0.9\, \text{g})\).

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\(^3\) All melting points are uncorrected.
\(^4\) F. Fischer : *Ber.*, 89, 2438 (1956).
The crystals were dissolved in AcOEt (40 mL) and stirred with 2N H₂SO₄ (44 mL) for 24 hr. at room temperature. The solution was extracted with AcOEt and the organic layer was washed with satd. NaHCO₃ solution, H₂O, 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 IIb, as crystals, m.p. 142°. Anal. Calcd. for C₁₇H₂₂O₆N: 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 (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 (17.0 g.) was dissolved in EtOH (200 mL) and MgSO₄ (21 g.) was added. To the mixture, a solution of K₂MnO₄ (25 g.) in H₂O (600 mL) was added during 1 hr. at -40~30°. After removing precipitating MnO₂ by filtration, the filtrate was evaporated and the residue was extracted with ether. The extract was dried with Na₂SO₄ and evaporated to afford an oil (12.5 g.). The oil was dissolved in MeOH (150 mL) and shaken with Pd-C prepared from 0.5% PdCl₂ (200 mL) and charcoal (3 g.) in an atmosphere of H₂. The catalyst was removed by filtration and the solvent was evaporated. To the residue, a small amount of H₂O 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. Anal. Calcd. for C₁₇H₂₃O₈: C, 71.02; H, 7.86. Found: C, 71.05; H, 7.85.

DL-erythro-1-Phenyl-1,2-propanediol (IXb)—N (15.2 g.) was added dropwise to a CHCl₃ solution of perbenzoic acid prepared from benzoyl peroxide (50 g.) at -10°. The solution was stirred for 50 hr. at 0°. The CHCl₃ solution was washed with FeSO₄ solution, 2N NaOH, H₂O and dried. Evaporation of the solution gave colorless crystals, to which 2N H₂SO₄ (90 mL) was added. The mixture was stirred for 40 hr. and extracted with ether. The extract was washed with satd. NaHCO₃ solution, H₂O, dried and evaporated to give an oil (13 g.). The oil (6 g.) was dissolved in MeOH (60 mL) and shaken with Pd-C prepared from 0.5% PdCl₂ (100 mL) and charcoal (1.4 g.) in an atmosphere of H₂. 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. 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 C₁₇H₂₃O₈: 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 was persued and Ia and Ib were assigned as threo and erythro forms respectively.

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