to give the residue which was recrystallized from benzene to provide 0.32 g. of XVI as hygroscopic white needles, m.p. 98°(picrate, 148~149°). *Anal.* Calcd. for $C_3H_5N_3 \cdot C_6H_3O_7N_3$ (picrate): C, 34.61; H, 2.56; N, 26.92. Found: C, 34.72; H, 2.70; N, 26.77. XVI was identified by IR spectral comparison and by admixture with an authentic sample prepared according to the method of Jones, *et al.*[3] and also by admixture of the picrate with that of the authentic sample.

Oxidation of XIII with Potassium Permanganate——To a suspension of 1.2 g. of XIII in 30 ml. of water, 4 g. of $KMnO_4$ dissolved in 200 ml. of water was added dropwise at 40~50° with stirring during one hour. After allowing the mixture to stand overnight with stirring, 1 g. of $KMnO_4$ dissolved in 50 ml. of water was further added. The mixture was allowed to stand overnight and the resulting MnO_2 was filtered off. The filtrate was concentrated to about ⅔ of its volume under a reduced pressure and extracted several times with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated to recover 0.34 g. of XIII. The aqueous layer was further concentrated to 100 ml. under a reduced pressure and adjusted to pH 3~4 with 2*N* HCl. By adding a saturated solution of copper acetate to this solution, bluish white precipitate was obtained, which was filtered, washed with water and dried. It was then suspended in 100 ml. of EtOH and the suspension was saturated with H_2S. The resulting CuS was filtered off and the filtrate was evaporated to dryness to give 0.75 g. of XV, m.p. 114°(decomp.). 0.5 g. of XV was heated in an oil bath, whereupon decomposition took place with evolution of CO_2 gas. The pyrolysis product was extracted with $CHCl_3$ and the solvent was evaporated to give the residue which was recrystallized from benzene to provide 0.24 g. of XVII as colorless needles, m.p. 117~118°. XVII was identified by IR spectral comparison and by admixture with an authentic sample prepared according to the procedure of Hoggarth, *et al.*[4]

Summary

s-Triazolo[1,5-*a*]pyridine ring was quite stable and showed properties similar to those of aromatic compounds. Nitration of 2-methyl-*s*-triazolo[1,5-*a*]pyridine (IV) with potassium nitrate and sulfuric acid gave two mononitro compounds (V) and (VI). Catalytic reduction of V and VI gave the corresponding amino derivatives (VII) and (VIII) which were further converted to the corresponding bromo derivatives (IX) and (X) by the Sandmeyer reaction. But this ring was quite unstable against oxidation and fission of the pyridine ring occurred to give *s*-triazole derivatives.

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UDC 547.568.1.07

75. Atsusuke Terada, Hiroo Itō, and Masatoshi Nagawa: Syntheses of 1-(*p*-Nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediols.*1

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

Kollonitsch[1] obtained an isomer of 1-(*p*-nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediol (I), as a crystalline substance of m.p. 163~165°, but he has not revealed that the substance is either DL-*threo* or DL-*erythro* form in which I exists.

In the present paper we wish to report that the two isomers of I were obtained by a method different from the Kollonitsch procedure.

Rebstock[2] reported that 2-bromo-3-methoxypropiophenone (II) was reacted with potassium phthalimide to yield 2-phthalimido-3-methoxypropiophenone (III), from

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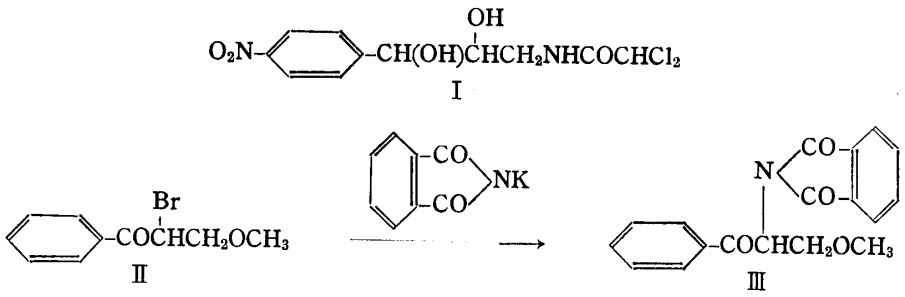
1) J. Kollonitsch, A. Hajos, M. Kraut, V. Gabor: Acta Chim. Acad. Sci. Hung., **6**, 381 (1955).

2) M. C. Rebstock: J. Org. Chem., **19**, 851 (1955).

which chloramphenicol was finally derived.



On the way to chloramphenicol from Ⅲ, the Meerwein Ponndorf reduction is involved. In such a case, it is known that the blockage of hydroxyl group by the methyl group affects the formation of the *erythro* form.[3] On the other hand, if a compound has the free hydroxyl group at the β position instead of the methoxy group in Ⅲ, the *threo* form is produced more predominantly than the *erythro* form owing to the bulky phthalimide group as reported in the previous paper.[4]

On this background, we planned to try the reduction of a compound having the hydroxyl group or a group which can be easily converted to the hydroxyl group instead of the methoxy group in Ⅲ. Therefore, to obtain 2-phthalimido-3-acetoxypropiophenone (Ⅶ) the reaction of 2-bromo-3-acetoxypropiophenone (Ⅵ) with potassium phthalimide was examined. However, the reaction did not give Ⅶ, but 2-acetoxy-3-phthalimidopropiophenone (Ⅺ), the position isomer of Ⅶ, involving 1,2-shift. Hence, the study is oriented to the conversion of Ⅺ to the position isomer (I) of chloramphenicol.

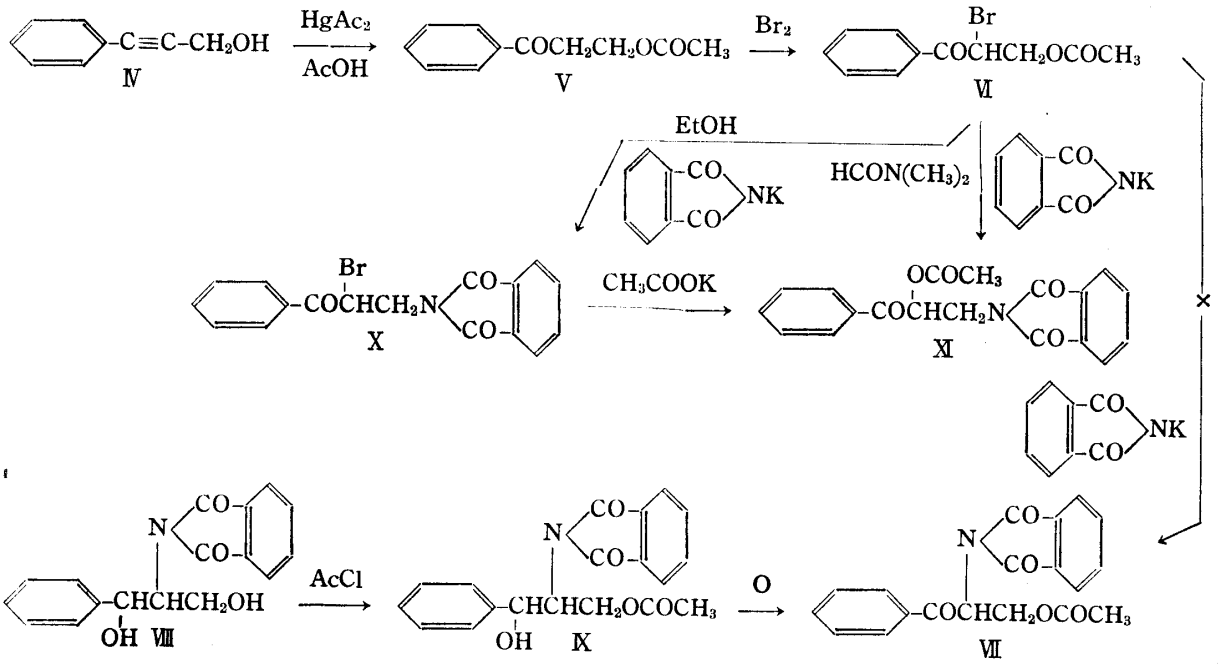


Chart 1.

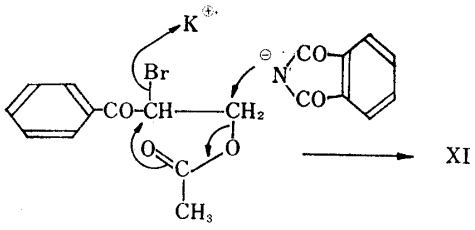
Ⅵ was obtained from the bromination of 3-acetoxypropiophenone (Ⅴ), which was afforded by refluxing 3-phenylpropargylalcohol (Ⅳ) in acetic acid under the presence of mercuric acetate in the application of the Matsoyan procedure.[5] Then Ⅵ was

3) J. Sicher, M. Svoboda, M. Hrda, J. Rudinger, T. Sorm : Chem. Listy, **47**, 565 (1953).
4) A. Terada, H. Itō, M. Nagawa : Ann. Sankyo Res. Lab., **15**, 36 (1963).

reacted with potassium phthalimide in dimethylformamide to give a substance of m.p. 133° in a good yield. The elementary analysis of the substance was identical with the formula of XI and the infrared spectra also suggested that it is XI.

Then in order to prove that the substance of m.p. 133° is not VII, DL-*threo*-1-phenyl-2-phthalimido-1,3-propanediol (VIII)[6] was reacted with acetylchloride to yield DL-*threo*-1-phenyl-2-phthalimido-3-acetoxy-1-propanol (IX). IX was oxidized by sodium bichromate to give VII as a compound of m.p. 118°, which was unidentical with XI. Thus, the substance of m.p. 133° was characterized as 2-acetoxy-3-phthalimidopropiophenone (XI), the position isomer of VII.

In the reaction VI→XI, the following two reaction mechanisms may be possible. The one is a mechanism that phthalimide anion attacks the β-carbon and simultaneously acetyl group is migrated to the α-carbon accompanying the removal of the bromine anion, as shown in the following figure. The other is a mechanism that the phthalimide anion attacks the β-carbon and then the resulting acetyl anion attacks the α-carbon followed to cause the removal of the bromine anion.



XI

If the reaction proceeds through the latter mechanism, 2-bromo-3-phthalimidopropiophenone (X) is to be produced as an intermediate.

After several attempts to find X, we found that X crystallized out from the ethanol solution, in which VI was reacted with potassium acetate in dimethylformamide to afford XI. Thus, the reaction VI→XI may be considered to occur by the latter reaction. However, it is not sound that the former mechanism is ruled out on the base of the finding, because X was found only when the reaction was carried out in ethanol, but not when in dimethylformamide.

When XI is submitted to catalytic reduction over palladium on charcoal, 1-phenyl-2-acetoxy-3-phthalimido-1-propanol (XII) is expected to be produced, but an oily product was obtained, which was not purified. Then XII was acetylated with acetic anhydride and pyridine to cause solidification. The solid mass was recrystallized from methanol to afford two kinds of crystals having m.p. 153~155° (XIIIa) and m.p. 175° (XIIIb) in approximately 50:50 weight ratio, each of which corresponded respectively to an isomer of 1-phenyl-3-phthalimido-1,2-propanediol diacetate (XIII). XIII was nitrated with nitric acid (s.w. 1.52) to yield 1-(*p*-nitrophenyl)-3-phthalimido-1,2-propanediol diacetate (XIV), as crystals of m.p. 179° (XIVa) from XIIIa and as an oil (XIVb) from XIIIb. When XIV was heated with hydrazine hydrate in methanol, the phthaloyl group was removed and then O-acetyl group migrated to nitrogen to give 1-(*p*-nitrophenyl)-3-acetamido-1,2-propanediol (XV), as crystals of m.p. 159~162° (XVa) from XIVa and crystals of m.p. 170~173° (XVb) from XIVb. The migration of O-acetyl group to nitrogen was assigned by the amido bands in the infrared spectrum. Then XV was deacetylated to yield 1-(*p*-nitrophenyl)-3-amino-1,2-propanediol(XVI), as crystals of m.p. 124~125° (XVIa) from XVa and as crystals of m.p. 142~143° (XVIb) from XVb. Finally XVI was reacted with methyl dichloroacetate to afford 1-(*p*-nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediol (I), as crystals of m.p. 161~163° (Ia) from XVIa and as crystals of m.p. 151~153° from XVIb.

The configuration of these isomers will be determined in the following paper[7].

Neither of the isomers of I showed any effective antibiotic activity for *St. aureus* and *E. Coli*.

5) S. Matsoyan, G. Chukhadzhyan, S. Vartanyan : Zhur. Obshcheri Khim., **30**, 1202 (1960).
6) A. Terada, H. Itō, M. Nagawa : Ann. Sankyo Res. Lab., **15**, 45 (1963).
7) A. Terada, H. Itō, M. Nagawa : This Bulletin, **14**, 533 (1966).

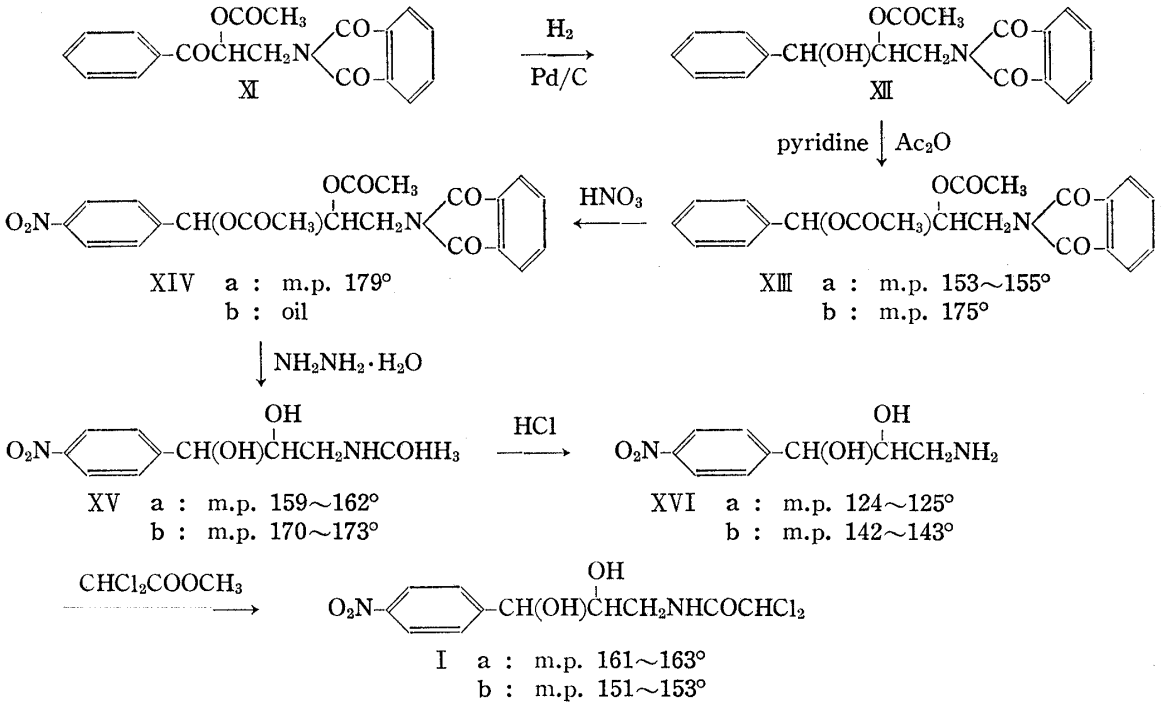


Chart 2.

Experimental*3

3-Acetoxypropiophenone (V)——AcOH (60 ml.) and $HgAc_2$ (3g.) were added to 3-phenylpropargyl alcohol (IV) (30 g.) and the mixture was refluxed for 8 hr. After evaporating AcOH, ice water was added to the residue and the mixture was extracted with AcOEt. The extract was washed with satd. $NaHCO_3$ solution, H_2O, dried and evaporated to afford an oil, b.$p_{0.2}$ 108~110°, which soon crystallized. Recrystallization from benzene gave V (28.5 g.), as needles of m.p. 61°. *Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.73; H, 6.34.

DL-*threo*-1-Phenyl-2-phthalimido-3-acetoxy-1-propanol (IX)——A solution of AcCl (0.9 g.) and $HCON(CH_3)_2$ (3 ml.) was added dropwise to a solution of VIII[6] (3 g.), $HCON(CH_3)_2$ (9 ml.) and dried pyridine (0.9 ml.). After heating for 40 min. at 50~55°, the solution was poured onto ice water. AcOEt and 10% HCl (50 ml.) were added to the solution and the organic layer was washed with satd. $NaHCO_3$ solution, H_2O, dried and evaporated to give colorless crystals. Recrystallization from MeOH afforded IX (2.4 g.), as plates of m.p. 128°. *Anal.* Calcd. for $C_{19}H_{17}O_5N$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.15; H, 5.24; N, 4.10.

DL-2-Phthalimido-3-acetoxypropiophenone (VII)——A solution of $Na_2Cr_2O_7$ (4 g.), H_2O (18 ml.), H_2SO_4 (5 ml.) and AcOH (2 ml.) was added to a solution of IX (1.8 g.) in CH_2Cl_2 (20 ml.) dropwise with stirring and allowed to stand for 3 hr. at room temperature. H_2O (10 ml.) was added to the mixture and then the organic layer was washed with 2.5% $NaHSO_3$ (20 ml.), 5% HCl, satd. $NaHCO_3$, H_2O, dried and evaporated to give an oily residue, which was recrystallized from MeOH to afford VII (1.2 g.), as needles of m.p. 118°. *Anal.* Calcd. for $C_{19}H_{15}O_5N$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.63; H, 4.59; N, 4.34. IR ν_{max}^{Nujol} cm^{-1}: 1790, 1755, 1722, 1693, 1392, 1225.

2-Bromo-3-phthalimidopropiophenone (X)——V (2 g.) was dissolved in dried ether (30 ml.) and a small amount of $AlCl_3$ was added and then bromine (1.7 g.) was added dropwise with stirring. The reaction mixture was poured onto ice water and extracted with AcOEt. The extract was washed with satd. $NaHCO_3$ solution, H_2O, dried and evaporated giving an oily residue. To the residue dissolved in EtOH (10 ml.) was added potassium phthalimide (3 g.). After stirring for 1 hr. at room temperature, the mixture was filtered and collected crystals were washed with H_2O. Recrystallization from MeOH gave X (2.8 g.), as needles of m.p. 112~113°. *Anal.* Calcd. for $C_{17}H_{12}BrO_3N$: C, 56.96; H, 3.35; N, 3.91. Found: C, 56.95; H, 3.56; N, 3.83.

2-Acetoxy-3-phthalimidopropiophenone (XI)——i) V (5 g.) was dissolved in dried ether (100 ml.) and a small amount of $AlCl_3$ was added and then bromine (4.6 g.) was added dropwise with stirring. The reaction mixture was poured onto ice water and extracted with AcOEt. The extract was washed with satd. $NaHCO_3$

*3 All melting points are uncorrected.

solution, H_2O, dried and evaporated to leave an oily residue, which was then dissolved in $HCON(CH_3)_2$ (20 ml.) and potassium phthalimide (5 g.) was added. After stirring for 1 hr., the reaction mixture was filtered and to the filtrate AcOEt and 10% HCl (100 ml.) were added. The organic layer was washed with satd. $NaHCO_3$ solution, H_2O, dried and evaporated to leave a crystalline residue, which was recrystillized from MeOH to give XI (7.5 g.), as plates of m.p. 133°. *Anal.* Calcd. for $C_{19}H_{15}O_5N$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.77; H, 4.59; N, 4.09. IR ν_{max}^{Nujol} cm^{-1}: 1787, 1755, 1720, 1695, 1395, 1225.

ii) A mixture of X (2 g.), CH_3COOK (0.8 g.), and $HCON(CH_3)_2$ (10 ml.) was heated for 1 hr. at 50°. After cooling, AcOEt and 10% HCl (50 ml.) were added. The organic layer was washed with satd. $NaHCO_3$ solution, H_2O, dried and evaporated to give a crystalline residue. Recrystallization from MeOH afforded plates (1.3 g.) of m.p. 133°, which was identical with XI obtained at i).

1-Phenyl-3-phthalimido-1,2-propanediol Diacetate (XIII)——XI (5 g.) was dissolved in MeOH (100 ml.) and shaken with Pd-C prepared from 0.5% $PdCl_2$ (25 ml.) and charcoal (1 g.) in an atmosphere of H_2. The catalyst was removed by filtration and the solvent was evaporated. To the residue Ac_2O (15 ml.) and dried pyridine (15 ml.) were added. After heating for 1 hr. at 100°, Ac_2O and pyridine were evaporated, and the residue was dissolved in MeOH. During concentrating, the solution afforded XIIIb (2.2 g.), as prisms of m.p. 175°. *Anal.* Calcd. for $C_{21}H_{19}O_6N$: C, 66.13; H, 5.02; N, 3.67. Found: C, 65.87; H, 5.14; N, 3.84.

After concentrating further, the methanolic liquor gave XIIIa (2.4 g.), as needles, m.p. 153~155°. *Anal.* Found: C, 65.87; H, 5.14; N, 3.84.

1-(*p*-Nitrophenyl)-3-phthalimidoi-1,2-propanediol Diacetate (XIV)——H_2SO_4 (5.5 ml.) was added to HNO_3 (d, 1.52) (5.5 ml.) under cooling and to this solution XIIIa (4 g.) was added in small portions at −10° within 30 min. After stirring for 2 hr. at 0°, the solution was poured onto ice water (150 g.). Precipitating crystals were extracted with AcOEt and evaporated to dryness. Recrystallization from MeOH gave XIVa (1.3 g.), as needles of m.p. 179°. *Anal.* Calcd. for $C_{21}H_{18}O_8N_2$: C, 59.15; H, 4.26; N, 6.57. Found: C, 59.10; H, 4.95; N, 6.56. IR ν_{max}^{Nujol} cm^{-1}: 1790, 1740, 1705, 1540, 1350.

XIIIb (5 g.) was worked up in the same manner as treatment of XIIIa to give an oil (5.3 g.).

1-(*p*-Nitrophenyl)-3-acetamido-1,2-propanediol (XV)——XIVa (2 g.), MeOH (40 ml.), and $NH_2NH_2 \cdot H_2O$ (2.5 ml.) were refluxed for 2 hr. The resulting crystal was filtered off and the filtrate was evaporated to dryness. A small amount of H_2O was added to the residue and extracted with AcOEt. The extract was dried and evaporated to give a crystlline residue. Recrystallization from MeOH afforded XVa (0.6 g.), m.p. 159~162°. *Anal.* Calcd. for $C_{11}H_{14}O_5N_2$: C, 51.96; H, 5.55; N, 11.02. Found: C, 52.19; H, 5.43; N, 11.46. IR ν_{max}^{Nujol} cm^{-1}: 3310, 1625, 1555, 1525, 1355, 1305, 1130, 1120.

XIVb (oil) (5.3 g.) was worked up in the same manner as treatment of XIVa to give crystals of m.p. 170~173° (1 g.). IR ν_{max}^{Nujol} cm^{-1}: 3350, 3210, 1650, 1560, 1520, 1360, 1305, 1095, 1055.

1-(*p*-Nitrophenyl)-3-amino-1,2-propanediol (XVI)——XVa (0.5 g.) was heated with 5% HCl for 1 hr. on a boiling water bath. The solution was adjusted to pH 10 with Na_2CO_3 and extracted with AcOEt and dried. Concentration of the solution afforded XVIa (0.25 g.), m.p. 124~125°. *Anal.* Calcd. for $C_9H_{12}O_4N_2$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.09; H, 5.70; N, 13.40. IR ν_{max}^{Nujol} cm^{-1}: 3490, 3480, 3200, 1550, 1305, 1110, 1090.

XVb (0.5 g.) was worked up in the same manner as treatment of XVa to give XVIb (0.3 g.), as colorless crystals, m.p. 142~143°. IR ν_{max}^{Nujol} cm^{-1}: 3410, 3325, 1520, 1352, 1115, 1053.

1-(*p*-Nitrophenyl)-3-(2,2-dichloroacetamido)-1,2-propanediol (I)——XVIa (0.25 g.), MeOH (2 ml.), and methyl dichloroacetate (2 ml.) were heated for 1 hr. at 55°. After evaporating MeOH, petr. ether was added to the residue to give colorless crystals. Recrystallization from CH_2Cl_2 afforded XVIIa (0.1 g.), m.p. 161~163°. *Anal.* Calcd. for $C_{11}H_{12}Cl_2O_5N_2$: C, 40.80; H, 3.71; N, 8.61; Cl, 22.01. Found: C, 40.90; H, 3.98; N, 8.41; Cl, 21.78. IR ν_{max}^{Nujol} cm^{-1}: 3405, 1665, 1505, 1355, 1130, 1120. XVIb (0.3 g.) was worked up in the same manner as treatment of XVIa to give XVIIb (0.15 g.), m.p. 151~153°. *Anal.* Found; C, 40.80; H, 3.79; N, 8.60; Cl, 21.89. IR ν_{max}^{Nujol} cm^{-1}: 3405, 3125, 1670, 1505, 1360, 1215, 1110.

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Summary

2-Bromo-3-acetoxypropiophenone (VI) was reacted with potassium phthalimide in dimethylformamide to give 2-acetoxy-3-phthalimidopropiophenone (XI). XI was submitted to hydrogenation over palladium on charcoal followed by acetylation with acetic anhydride and pyridine to yield two DL-isomers of 1-phenyl-3-phthalimido-1,2-propanediol diacetate (XIII).

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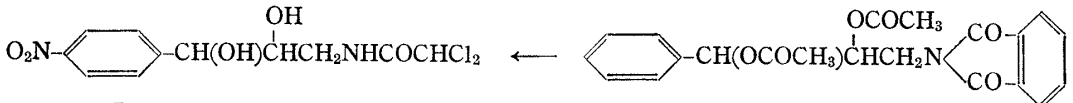
76. Atsusuke Terada, Hiroo Itō, and Masatoshi Nagawa : Determination of Configurations of the Two DL-Isomers of 1-(*p*-Nitrophenyl)-3-(2, 2-dichloroacetamido)-1, 2-propanediols.*1

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

In the preceding paper[1] 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 paper[1], 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 Gensler[3] 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

*1 Reported at the 82th Annual Meeting of the Pharmaceutical Society of Japan, Shizuoka, 1962.
*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).