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186. Shun-ichi Yamada, Kenji Koga, and Hisayuki Matsuo : Studies on Optically Active Amino Acids. IV.*1 A New Synthetic Approach to Chloramphenicol Base*2 from L-Phenylalanine.

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So far as the synthesis of optically active compound is carried out with the racemic starting material, resolution of the product is usually inevitable at some stage of the synthetic route. The choice of a suitable optically active compound as a starting material, however, will afford the optically active objective without resolution, if the diastereomers that will be produced owing to the newly created asymmetric carbon atom can be separated or the reaction is effected stereoselectively. Moreover, if the configuration of the newly created asymmetric carbon atom can be deduced relative to the known configuration of the asymmetric center which is the same as that of the starting meterial, absolute configuration of the synthesized compound becomes clear. It seemed very interesting and important to put this concept for synthesis into practice and the optically active α-amino acids, which are now being produced cheaply, are considered to be one of the most suitable starting materials for this purpose.

Chloramphenicol (D(−)*threo*-2-dichloroacetamido-1-*p*-nitrophenyl-1, 3-propanediol or L_S(−)*threo*-N-dichloroacetyl-3-*p*-nitr ophenylserinol*2) (I) is one of the most useful antibiotics and, as shown in Chart1, itsabsolute configuration is already known,[1] and many synthetic approaches have been extensively investigated.[2] By comparing I with L-phenylalanine (II), it is clear that the configuration of C-2 in I is the same as that of the α-carbon in II. This paper concerns the new synthetic approach to chloramphenicol base starting with II, making use of the same configuration of the α-carbon in II as that of the C-2 in I.

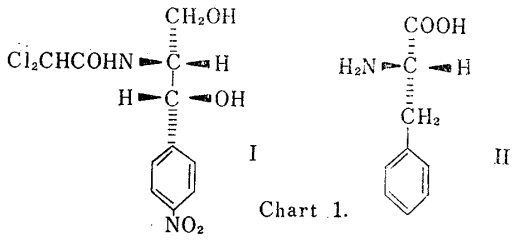
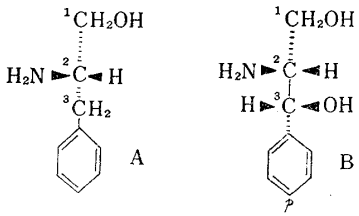


Chart 1.

*1 Part III : This Bulletin, **10**, 693 (1962).

*2 To avoid confusion in nomenclature, all compounds that appear in this paper are considered as having the parent skeleton of A or B, which are named and numbered as follows :
(A) L_S-3-Phenylalaninol
(B) L_S-*threo*-3-Phenylserinol



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1) *a*) M.C. Rebstock, H.M. Crooks, Jr., J. Controulis, Q.R. Bartz : J. Am. Chem. Soc., **71**, 2458 (1949). *b*) G. Fodor, J. Kiss, I. Sallay : J. Chem. Soc., **1951**, 1858. *c*) M. Honjo : Yakugaku Zasshi, **73**, 368 (1953). *d*) D. Fleš, B. Balenović : J. Am. Chem. Soc., **78**, 3072 (1956).

2) For general references : *a*) Y. Sumiki : "Kōsei Busshitsu," Vol. 1. 403~543 (1961). Tokyo Univ. Press, Tokyo. *b*) M. Suzuki : Ann. Takamine Lab., **11**, 1~26 (1959); *Idem* : J. Antibiotics (Japan), Ser. B, **14**, 323~345 (1961).

First, we started with DL-phenylalanine (III), for the purpose of getting a suitable route, which is shown in Chart 2 (suffix a). DL-Phenylalanine ethyl ester (IVa) was reduced with lithium aluminum hydride or sodium borohydride to the corresponding DL-3-phenylalaninol[3a] (Va). It is very interesting that IVa is reduced to Va by sodium borohydride in a good yield.*4 The reaction of its diacetate (VIa) with N-bromosuccinimide in carbon tetrachloride, however, did not materialize. Considering that the presence of NH group of the amide might inhibit the reaction, Va was phthaloylated to DL-N-phthaloyl-3-phenylalaninol (VIIa) by heating with equimolar amount of N-ethoxycarbonylphthalimide[4] in pyridine. VIIa was then benzoylated to the corresponding 1-O-benzoate (VIIIa). The reaction of VIIIa with N-bromosuccinimide proceeded smoothly to afford the objective bromides (IXa), which were separated into two diastereomers by fractional recrystallizations. Heating both these diastereomers of IXa with fused potassium acetate in glacial acetic acid-acetic anhydride mixture gave the corresponding acetates (Xa), though this acetolysis reaction was not stereospecific. Separation of diastereomers by column chromatography and by fractional recrystallizations afforded two isomers, m.p. 121~122° and m.p. 156~157°, though their yields were poor owing to repeated recrystallizations. The diastereomeric mixture (Xa) was then nitrated in fuming nitric acid to the *p*-nitro derivative (XIa). Chromatographic separation of this mixture of

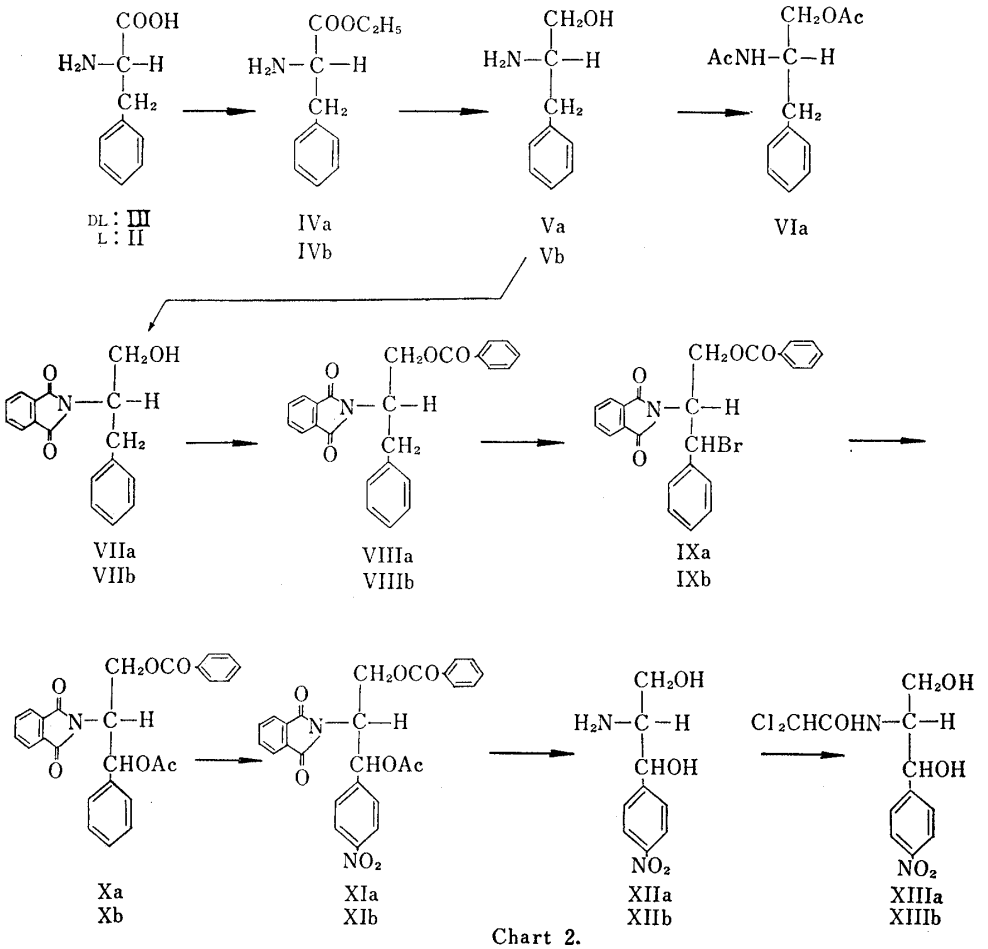

Chart 2.

*4 Details of this reduction will be published later.

3) *a*) P. Karrer, P. Portmann, M. Suter : Helv. Chim. Acta, **31**, 1617 (1948). *b*) J. H. Hunt, D. McHale: J. Chem. Soc., **1957**, 2073.

4) G. H. L. Nefkens : Nature, **185**, 309 (1960); G. H. L. Nefkens. G. I. Tesser, R. J. F. Nivard : Rec. trav. chim., **79**, 688 (1960).

diastereomers (XIa) on Florisil column gave two isomers, m.p. 154~157° and m.p. 183~190°, but the separation was neither complete nor quantitative. The diastereomeric mixture (XIa) was then treated with hydrazine, followed by hydrolysis, and the resulting free amine (XIIa) was heated with methyl dichloroacetate to afford a mixture of diastereomers of the corresponding N-dichloroacetyl derivative (XIIIa). Recrystallizations of this mixture (XIIIa) gave colorless crystals of m.p. 151~153.5° and its infrared spectrum in dioxane solution was identical with that of the authentic commercial chloramphenicol.

As the synthetic route was thus established for the racemic compounds, the same reactions were carried out starting with L-phenylalanine (II) (Chart 2, suffix b). As was expected, the reactions proceeded almost equally as in the case of racemic compounds except in the last stage, where the separation of diastereomers of XIIIb was not successful.

Taguchi, *et al.*[5d] described the acyl rearrangement reaction on a mixture of DL-*threo*- and DL-*erythro*-N-benzoyl-3-phenylserinol leading to the corresponding DL-*threo* isomer. This reaction is well corroborated with other works.[5] Application of this stereoselective rearrangement is expected to convert the mixture of *threo*- and *erythro*-(XIIb) to the *threo* isomer, whose configuration is the same as that of chloramphenicol.

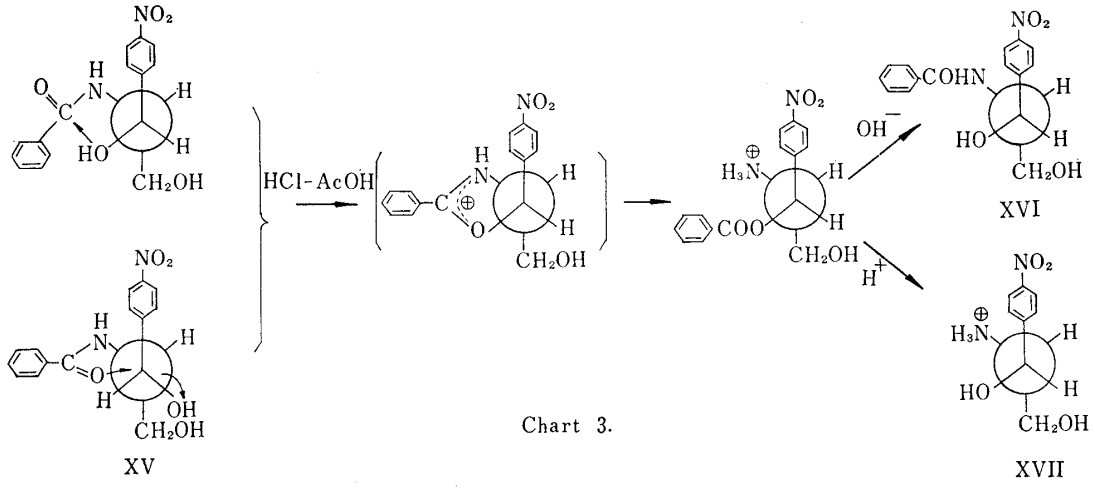

Chart 3.

In the case of N, 1-O-diacetate (XIV), this stereoselective rearrangement did not proceed with success, probably due to hydrolysis before the rearrangement. In the case of N-benzamide (XV), however, hydrolysis was not observed, and XVI and XVII were obtained by the known method.[5d] They were proved to be identical with the authentic samples[1a, 5e] derived from commercial chloramphenicol, through mixed melting point test, and infrared spectral and paper chromatographic data.

Experimental*5

Syntheses Starting with DL-Phenylalanine (III)

DL-Phenylalanine Ethyl Ester (IVa)——Prepared according to Brenner's method[6] with some modifications as follows: To a stirred, ice-cold suspension of III (30 g., 0.182 mole) in abs. EtOH (800 ml.), $SOCl_2$

*5 All melting points and boiling points are not corrected. Infrared spectra were measured with Koken DS-301 spectrophotometer and optical rotations were measured with Zeiss Kreispolarimeter.

5) *a*) L.H. Welsh: J. Am. Chem. Soc., **69**, 128 (1947); *Ibid.*, **71**, 3500 (1949). *b*) G. Fodor, J. Kiss: Nature, **163**, 287 (1949); G. Fodor, J. Kiss, I. Sallay: *Ibid.*, **167**, 690 (1951). *c*) M. Miyamoto: Yakugaku Zasshi, **72**, 677 (1952). *d*) T. Taguchi, M. Tomoeda, H. Fukuyama: This Bulletin, **4**, 80 (1956). *e*) S. Ikuma: Yakugaku Zasshi, **79**, 937 (1959).

6) M. Brenner, W. Huber: Helv. Chim. Acta, **36**, 1109 (1953). cf. E. Taschner, C. Wasielewski: Ann., **640**, 136 (1961).

(32.5 g., 0.273 mole) was added dropwise, the reaction mixture was then refluxed for 3.5 hr., and the pale yellow solution was allowed to stand at room temperature overnight. EtOH was evaporated *in vacuo* to leave colorless crystals, which were dissolved in cold H_2O, basified with excess K_2CO_3, and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried over anhyd. Na_2SO_4. On evaporation of Et_2O there remained pale yellow oil, which was distilled under reduced pressure to give IVa (26.3 g., 75%) as a colorless liquid of $b.p_{10}$ 140~142°. The ester thus obtained was identified through IR spectral data with the specimen prepared by Fischer's method[7] (yield, 62%).

DL-3-Phenylalaninol (Va)——a) Reduction of IVa with $LiAlH_4$[3a]: Colorless crystals of m.p. 66~67° (reported[3a] m.p. 67~68°) were obtained in 68% yield.

b) Reduction of the hydrochloride of IVa with $NaBH_4$*[4]: A mixture of IVa hydrochloride (3.0 g., 0.013 mole) in abs. EtOH (25 ml.) and $NaBH_4$ (3.0 g., 0.079 mole) in abs. EtOH (100 ml.) was refluxed for 25 hr. Evaporation of EtOH *in vacuo* gave a residue, which was dissolved in H_2O and extracted with AcOEt. The AcOEt solution was shaken with sat. NaCl solution, dried, and evaporated to afford Va (1.6 g., 81%) as colorless crystals of m.p. 64~65°. This sample was proved to be identical with the specimen prepared in a) by comparing their IR spectra.

DL-N-Phthaloyl-3-phenylalaninol (VIIa)——A solution of Va (1.5 g., 0.01 mole) and N-ethoxycarbonylphthalimide[4] (2.2 g., 0.01 mole, m.p. 90~91°) in pyridine (55 ml.) was refluxed for 2.5 hr. and kept standing at room temperature overnight. Pyridine was evaporated *in vacuo* and the residue was taken up in AcOEt, which was washed successively with 5% HCl, 5% NaOH, and H_2O. After drying over anhyd. Na_2SO_4, AcOEt was evaporated under reduced pressure to leave a white solid, which was recrystallized from benzene-hexane to afford VIIa (2.2 g., 79%), as colorless needles of m.p. 97~98°. IR ν_{max}^{Nujol} cm^{-1}: 3460 (OH), 1770 (sh), 1695 (phthalimide). *Anal.* Calcd. for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.69; H, 5.76; N, 4.64.

DL-N-Phthaloyl-3-phenylalaninol 1-O-Benzoate (VIIIa)——To a solution of VIIa (1.3 g., 0.0046 mole) in pyridine (10 ml.), BzCl (0.8 g., 0.0057 mole) was added and the whole was worked up as usual. Recrystallization from EtOH gave VIIIa (1.3 g., 78%) as colorless needles, m.p. 119.5~121°. IR ν_{max}^{Nujol} cm^{-1}: 1776 (sh), 1712 (phthalimide), 1706, 1292 (benzoate). *Anal.* Calcd. for $C_{24}H_{19}O_4N$: C, 74.79; H, 4.97; N, 3.63. Found: C, 74.63; H, 5.06; N, 3.84.

Reaction of VIIIa with N-Bromosuccinimide——To a mixture of N-bromosuccinimide (0.93 g., 0.0052 mole) and VIIIa (2.0 g., 0.0052 mol.) in CCl_4 (70 ml.), a small amount of benzoyl peroxide was added and the whole was refluxed until all succinimide crystallized out (40 min.). The reaction mixture became pale brown at the end of the reaction. After cool, the reaction mixture was filtered and washed with a small amount of cold CCl_4. The filtrate and CCl_4 washings were combined and evaporated to afford a pale yellow oil, which was dissolved in benzene. Hexane was added to this solution until turbidity appeared and the whole was allowed to stand in a refrigerator overnight. The crystals that deposited were recrystallized from EtOH to colorless prisms (series-A) (1.0 g., 41.5%), m.p. 140~143°. Repeated recrystallizations from EtOH raised the melting point to 143~144°. IR ν_{max}^{Nujol} cm^{-1}: 1777 (sh), 1761 (sh), 1735, 1719 (phthalimide and benzoate), 1275 (benzoate).

The mother liquor of the above benzene-hexane recrystallization was evaporated to leave pale yellow oil, which crystallized on scratching. Recrystallization from EtOH gave another isomer (series-B) (1.0 g., 41.5%) of colorless prisms, m.p. 102~103°. IR ν_{max}^{Nujol} cm^{-1}: 1782 (sh), 1734, 1720 (phthalimide and benzoate), 1279 (benzoate). *Anal.* Calcd. for $C_{24}H_{18}O_4NBr$: C, 62.08; H, 3.91; N, 3.02. Found (in series-A): C, 61.68; H, 4.04; N, 3.15. Found (in series-B): C, 61.99; H, 4.11; N, 3.14.

DL-N-Phthaloyl-3-phenylserinol 1-O-Benzoate 3-O-Acetate (Xa)——a) A mixture of IXa (series-A) (1.6 g., 0.0034 mole) and fused AcOK (0.52 g., 0.0052 mole) in glacial AcOH (100 ml.) and Ac_2O (5 ml.) was refluxed for 15 hr. and then evaporated to dryness. The residue was extracted with AcOEt, which was washed successively with H_2O, 5% Na_2CO_3, and H_2O. On evaporation of the dried extract there remained an oily substance, which solidified on scratching. Recrystallization from benzene-hexane gave a colorless solid (1.2 g., 80%) of m.p. 98~108°. This seemed to be a mixture of diastereomers and repeated recrystallizations from the same solvent gave a small amount of one isomer, m.p. 121~122°. IR ν_{max}^{Nujol} cm^{-1}: 1778 (sh), 1746, 1726, 1714 (phthalimide, benzoate and acetate), 1283 (benzoate), 1230 (acetate). *Anal.* Calcd. for $C_{26}H_{21}O_6N$: C, 70.42; H, 4.77; N, 3.16. Found: C, 70.30; H, 4.70; N, 3.22.

b) A mixture of IXa (series-B) (4.2 g., 0.0091 mole) and fused AcOK (1.35 g., 0.0138 mole) in glacial AcOH (190 ml.) and Ac_2O (10 ml.) was treated as above to afford a colorless solid (3.4 g., 85%) of m.p. 90~124°. This seemed to be a mixture of diastereomers. Chromatography of this sample on Al_2O_3 caused hydrolysis of the acetate group (absorption at 3480 cm^{-1} appeared and absorption near 1240 cm^{-1} disappeared in its IR spectrum). The initially eluted part (m.p. 136~138° when recrystallized from AcOEt-hexane) was then treated with Ac_2O-pyridine in the usual manner and recrystallized from benzene-hexane to give colorless needles of the other isomer, m.p. 156~157°. IR ν_{max}^{Nujol} cm^{-1}: 1780 (sh), 1733,

7) E. Fischer, W. Schöller: Ann., **357**, 1 (1907).

1717 (phthalimide, benzoate and acetate), 1286 (benzoate), 1254 (acetate). *Anal.* Calcd. for $C_{26}H_{21}O_6N$: C, 70.42; H, 4.77; N, 3.16. Found: C, 70.66; H, 4.51; N, 2.88.

DL-N-Phthaloyl-3-*p*-nitrophenylserinol 1-O-Benzoate 3-O-Acetate (XIa)——Nitration of Xa (1.6 g., m.p. 98~120°) was carried out in fuming nitric acid (6 ml.) at −20° (Rebstock's condition).[8] The reaction mixture was poured into ice-water to give a semi-solidual precipitation, which was taken up in AcOEt. The AcOEt layer was washed with sat. $NaHCO_3$ solution, H_2O, and dried over anhyd. Na_2SO_4. Evaporation of AcOEt gave a colorless liquid (1.6 g., 91%). IR $\nu_{max}^{Capl.}$ cm^{-1}: 1526, 1352 (nitro). This sample (920 mg.) was chromatographed on 85 g. of Florisil with the solvent system of $CHCl_3$–AcOEt (1:1). The initially eluted part (280 mg.) was recrystallized from AcOEt-hexane to a small amount of crystals, m.p. 154~157°, while the finally eluted part (170 mg.), when recrystallized from benzene-hexane, gave a small amount of crystals of m.p. 183~190°. Complete separation of diastereomers was not successful.

DL-3-*p*-Nitrophenylserinol (XIIa)——A solution of XIa (640 mg., 0.0013 mole, above-obtained liquid) and anhyd. NH_2NH_2 (42 mg.. 0.0013 mol.) in EtOH (50 ml.) was refluxed for 3.5 hr., and then evaporated to dryness. 18% HCl (50 ml.) was added to this residue and the whole was refluxed with stirring for 5 hr. and filtered. The filtrate was refluxed for further 8 hr. to complete hydrolysis and then evaporated to dryness. The residue was dissolved in H_2O, basified with excess K_2CO_3, and extracted with Et_2O, which was dried and evaporated to leave a yellowish brown liquid (190 mg., 69%). This was used for the next step without further purification. IR ν_{max}^{KBr} cm^{-1}: ~3400 (NH and OH), ~1050 (OH).

DL-*threo*-N-Dichloroacetyl-3-*p*-nitrophenylserinol (*rac*-Chloramphenicol) (XIIIa)——A mixture of XIIa (400 mg., 0.0019 mole) and methyl dichloroacetate (300 mg., 0.0021 mole) in MeOH (5 ml.) was refluxed for 1.5 hr. and then evaporated to dryness. The residue was treated with charcoal in hot EtOH and then recrystallized once from AcOEt-hexane, twice from H_2O to give colorless needles of m.p. 151~153.5° (reported[1a] m.p. 150~151°). Its IR spectrum in dioxane solution was identical with that of the authentic commercial chloramphenicol. *Anal.* Calcd. for $C_{11}H_{12}O_5N_2Cl_2$: C, 40.89; H, 3.74; N, 8.67. Found: C, 41.22; H, 3.70; N, 8.93.

Syntheses Starting with L-Phenylalanine (II)*[6]

L-Phenylalanine (II)*[7]——$[\alpha]_D^{14}$ −31° (c=1.036, H_2O).

L-3-Phenylalaninol (Vb)——a) Reduction with $LiAlH_4$[3a]: m.p. 93~94° (yield, 65%), $[\alpha]_D^{14}$ −17.4° (c=2.072, EtOH).

b) Reduction with $NaBH_4$*[4]: m.p. 93~94°, $[\alpha]_D^{23}$ −25.3° (c=2.02, EtOH) (reported[3b] m.p. 90~91°, $[\alpha]_D^{23}$ −24.7° (EtOH)).

L-N-Phthaloyl-3-phenylalaninol (VIIb)——m.p. 108.5~110° (yield, 88%), $[\alpha]_D^{18}$ −108° (c=2.442, EtOH). *Anal.* Calcd. for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.25; H, 5,63; N, 4.88.

L-N-Phthaloyl-3-phenylalaninol 1-O-Benzoate (VIIIb)——m.p. 90~92° (yield, 81%), $[\alpha]_D^{18}$ −47.6° (c=1.680, benzene). *Anal.* Calcd. for $C_{24}H_{19}O_4N$: C, 74.79; H, 4.97; N, 3.63. Found: C, 75.15; H, 5.28; N, 3.48.

L-N-Phthaloyl-3-bromo-3-phenylalaninol 1-O-Benzoate (IXb)——A mixture of VIIIb (3.20 g., 0.0083 mole), N-bromosuccinimide (1.50 g., 0.0083 mole), and a small amount of benzoyl peroxide in CCl_4 (110 ml.) was treated as in the case of IXa to afford a pale yellow oil (3.64 g., 95%). All effort to solidify and separate diastereomers was not successful. $[\alpha]_D^{23}$ −24° (c=5.010, benzene).

L-N-Phthaloyl-3-phenylserinol 1-O-Benzoate 3-O-Acetate (Xb)——m.p. 117~124° (yield, 70%), $[\alpha]_D^{14}$ −11.4° (c=1.050, EtOH). Separation of diastereomers was not successful. IR ν_{max}^{KBr} cm^{-1}: 1785 (sh), 1738~1724 (phthalimide, benzoate and acetate), 1278 (benzoate), 1235 (acetate). *Anal.* Calcd. for $C_{26}H_{21}O_6N$: C, 70.42; H, 4.77; N, 3.16. Found: C, 70.02; H, 4.86; N, 3.37.

L-N-Phthaloyl-3-*p*-nitrophenylserinol 1-O-Benzoate 3-O-Acetate (XIb)——Pale yellow oily substance (mixture of diastereomers) (yield, 95%). $[\alpha]_D^{25}$ −7° (c=1.006, benzene). IR $\nu_{max}^{Capil.}$ cm^{-1}: 1534, 1352 (nitro).

L-3-*p*-Nitrophenylserinol (XIIb)——Pale yellow oily substance (mixture of diastereomers) (yield, 60%). IR $\nu_{max}^{Capil.}$ cm^{-1}: ~3400 (NH and OH), ~1050 (OH).

L-N-Dichloroacetyl-3-*p*-nitrophenylserinol (XIIIb)——A solution of XIIb (1.07 g., 0.005 mole) and methyl dichloroacetate (800 mg., 0.0056 mole) in MeOH (15 ml.) was refluxed for 1.5 hr., and evaporated to dryness. The pale red oily residue was treated with charcoal in hot EtOH and then recrystallized from AcOEt-hexane to a colorless solid (1.0 g., 61%) of m.p. 150~154°. Repeated recrystallizations from H_2O gave colorless needles of m.p. 164~166°. Isolation of the *threo*-isomer (reported[1a] m.p. 150~151°) was not successful. IR ν_{max}^{Nujol} cm^{-1}: 3280, 3100 (OH and NH), 1675, 1565 (amide). 1518, 1348 (nitro),

*[6] Unless otherwise stated, optically active compounds were prepared in the same way as in the case of the corresponding racemic compounds.

*[7] In this experiment, the same lot L-phenylalanine was used.

8) M.C. Rebstock: J. Org. Chem., **19**, 851 (1954).

1092, 1052 (OH), 808 (*p*-substituted phenyl). *Anal.* Calcd. for $C_{11}H_{12}O_5N_2Cl_2$: C, 40.89; H, 3.74; N, 8.67. Found: C, 41.12; H, 4.06; N, 8.75.

L-N-Benzoyl-3-*p*-nitrophenylserinol (XV)——To a mixture of 10% NaOH (5 ml.), Et_2O (30 ml.), and XIIb hydrochloride (250 mg., 0.001 mole), BzCl (300 mg., 0.0022 mole) in Et_2O (10 ml.) was added and the whole was shaken vigorously for 1 hr. Et_2O (100 ml.) was added to this and the separated Et_2O layer was washed with 10% NaOH, H_2O, dried, and evaporated. The residue (410 mg.) was treated with 0.4% NaOH-MeOH (50 ml.) under reflux for 1 hr. On evaporation of MeOH *in vacuo* there remained a red oil, which was extracted with $CHCl_3$, washed with H_2O, dried and evaporated. The residue was treated with charcoal in hot EtOH and EtOH was evaporated to leave a yellow oily substance (220 mg., 70%). IR ν_{max}^{KBr} cm^{-1}: 3400~3300 (OH and NH), 1640, 1565 (amide), 1520, 1350 (nitro), ~1050 (OH).

Acyl Rearrangement Reaction on XV——a) A mixture of XV (210 mg.), conc. HCl (0.75 g.), and glacial AcOH (1.5 g.) was boiled at 125~130° (bath temperature) for 5 min. (Taguchi's condition).[5d] Evaporation of the mixture *in vacuo* gave a viscous red oil, which was dissolved in ca. 5 ml. of H_2O. After separation of some insoluble materials by filtration, the filtrate and ca. 1 ml. of H_2O washings were combined and basified with 10% NaOH. The solid that deposited was taken up in AcOEt, which was washed with H_2O and dried over anhyd. Na_2SO_4. Evaporation of AcOEt gave a viscous oil (200 mg.), which was crystallized twice from AcOEt-hexane to white crystals (100 mg., 48%) of m.p. 163~166°. Further purification did not raise the melting point. This sample was proved to be identical with the authentic sample (m.p. 170~171°) derived from commercial chloramphenicol, through mixed melting point test and by IR spectral and paper chromatographic comparison. $[\alpha]_D^{18}$ −129.6° (c=0.52, dimethylformamide) (reported[5e] $[\alpha]_D^{25}$ −139.5° in the same solvent). Rf: 0.95 (BuOH-AcOH-H_2O (4:1:2)); 0.70 (2.5% AcOH-BuOH saturated with H_2O). *Anal.* Calcd. for $C_{16}H_{16}O_5N_2$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.38; H, 5.39; N, 8.74.

b) A mixture of XV (700 mg.), conc. HCl (2.25 g.) and glacial AcOH (4.5 g.) was boiled for 5 min. and then evaporated to dryness. The residue was treated with 18% HCl (50 ml.) under reflux for 8 hr. and the solution was treated with charcoal. The filtrate and H_2O washings were combined, washed with Et_2O, and evaporated to leave a pale brown oil, which was recrystallized from PrOH to afford colorless crystats (300 mg., 54%) of m.p. 201~204.5°. Recrystallization from PrOH gave colorless rods of m.p. 207~209°. Admixture with the authentic sample (m.p. 207~209°), derived from commercial chloramphenicol, showed no depression of melting point, and their IR spectra were in good agreement with each other. $[\alpha]_D^{18}$ −25.5° (c=1.920, MeOH) (reported[1a] $[\alpha]_D^{26.8}$ −26.9° in the same solvent). *Anal.* Calcd. for $C_9H_{13}O_4N_2Cl$: C, 43.47; H, 5.27; N, 11.27. Found: C, 43.80; H, 5.54; N, 10.86.

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Summary

A new synthetic approach to chloramphenicol base (XVII) was investigated starting with L-phenylalanine (II), making use of the same configuration of the α-carbon in (II) as that of the C-2 in XVII. Preliminary experiments starting with DL-phenylalanine was also described. The synthetic route is shown in Chart 2. *threo*-XVI and *threo*-XVII, the final product in this synthetic approach, were isolated from the mixture of *threo*- and *erythro*-XV by the application of the stereoselective acyl rearrangement reaction, which is shown in Chart 3.

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