Gas chromatographic peak of the latter was identical with that of Ⅷ obtained above a). NMR τ : 2.75, 2.82 (liquid) (integrated ratio 5:1), 2.67, 2.75 (in CCl_4) (integrated ratio 5:1) (=CH-O-). *Anal.* Calcd. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97; O, 31.64. Found : C, 59.21; H, 8.65; O, 31.98.

Elimination of Ethyl Alcohol from IX——One drop of conc. H_2SO_4 was added to 2.0 g. of Ⅸ and distilled under the mild reduced pressure (<30 mm. Hg) to distilled off EtOH. The residue was dissolved in benzene and washed with dil. K_2CO_3. Benzene solution was dried and concentrated to give the oil, which was distilled at $b.p_{0.6}$ 64~78° (0.6 g.). This oil exhibited the peaks at the retention time of 4.3 min. due to Ⅸ and that of 9.2 min. (condition c[*4]), which was found to be identical with that of Ⅷ. NMR τ : 2.67 (=CH-O-).

The authors express their deep gratitude to Prof. M. Tomita, Prof. S. Uyeo of Kyoto University, Prof. S. Nagakura of University of Tokyo, and Dr. K. Takeda, Director of this laboratory for their encouragement. Thanks are also due to Drs. H. Watanabe and K. Tori for their helpful discussion on the dipole moment and the NMR spectra. Gas chromatographic operation was carried out by Miss Y. Sato and Mr. K. Okuno, to whom the authors are grateful. They are also indebted to Mr. T. Ishiba for his technical assistance.

Summary

cis- and *trans*-2-Methoxymethylene-3-ethoxypropionitrile and 2-ethoxymethylene compounds are successfully separated and their structures were determined. Corresponding ester derivatives were not able to separate, however, the ratio of *cis/trans*-formation was made clear by elimination of ethyl alcohol from corresponding acetal compounds.

(Received August 6, 1965)

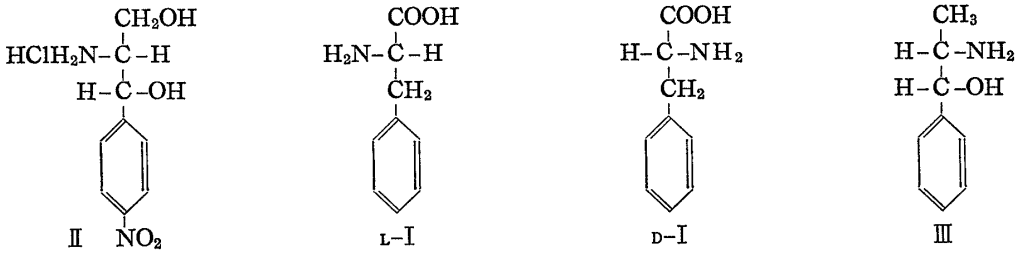
[Chem. Pharm. Bull. 14(3) 243~246 (1966)]

UDC 547.466.2.04 : 541.65

36. Kenji Koga,[*1] Hisayuki Matsuo,[*2] and Shun-ichi Yamada[*1] : Studies on Optically Active Amino Acids. VII.[*3] Stereoselective Synthesis of *l*-Norephedrine Hydrochloride from D-Phenylalanine.[*4]

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

In Part Ⅳ[1] of this series, the present authors reported the synthesis of chloramphenicol base hydrochloride (Ⅱ) from L-phenylalanine (L-I), by making use of the comparable configuration at the α-carbon in L-I with the asymmetric center bearing the



Ⅱ L-I D-I Ⅲ

Chart 1.

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[*3] Part Ⅵ : This Bulletin, **13**, 1399 (1965).

[*4] Presented at the 84th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1964.

1) S. Yamada, K. Koga, H. Matsuo : This Bulletin, **11**, 1140 (1963).

amino group in II, and introducing hydroxyl group at the benzylic position stereoselectively. Considering that the asymmetric carbon atom bearing the amino group in *l*-norephedrine (III) is comparable with that of D-phenylalanine (D-I), the present authors carried out the synthesis of *l*-norephedrine hydrochloride (XI) from D-phenylalanine (D-I). The synthetic route is shown in Chart 2. D-Phenylalanine (D-I) is now being obtained as a by-product in the synthetic production of L-phenylalanine (L-I), and used as the starting material for L-phenylalanine (L-I) through racemization.

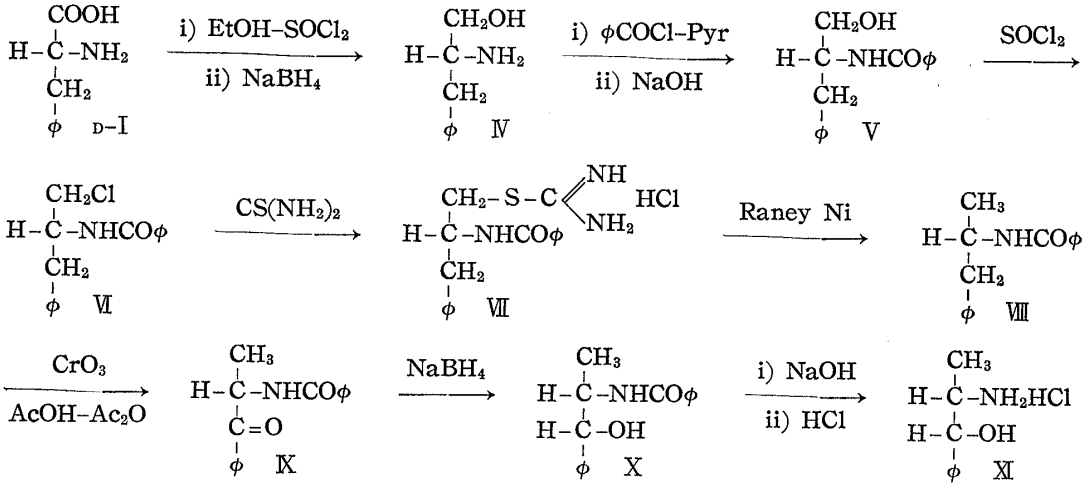

Chart 2.

D-Phenylalanine (D-I), $[\alpha]_D^{24}$ +31.6° (H_2O), was esterified and reduced with sodium borohydride in the usual manner[2] to the corresponding amino-alcohol (IV). The conversion of the hydroxymethyl group in IV to the methyl group was effected by reductive desulfurization of the thiopseudourea derivative (VII), prepared via the chloride (VI), to (*S*)-N-(α-methylphenethyl)benzamide (VIII), $[\alpha]_D^{25}$ +64.5° (EtOH). The oxidation of VIII with chromium trioxide in cold acetic acid-acetic anhydride mixture gave the objective ketone (IX), m.p. 105~106°, $[\alpha]_D^{21}$ +5° (EtOH). Though this ketone (IX) has a small specific rotation and the same melting point as the corresponding racemic ketone (XII), the fact that the infrared spectra of IX and XII are different in the solid state, that a mixed sample of IX and XII shows depression of the melting point, and also the results of subsequent reactions clearly show that this oxidation reaction was effected without any racemization.

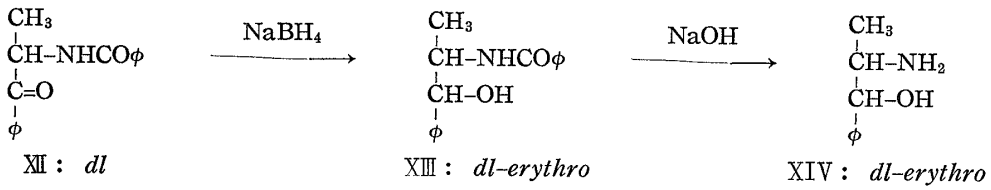

Chart 3.

Sodium borohydride reduction was conducted preliminarily with the racemic ketone (XII) to examine the stereoselectivity of this reaction. As a result, N-benzoyl-*dl*-norephedrine (XIII), m.p. 143~144°, was isolated in 70% yield. Hydrolysis of XIII with potassium hydroxide in aqueous ethanol afforded *dl*-norephedrine (XIV), which was identified with the authentic sample by mixed melting point determination. The

2) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, S. Yamada : This Bulletin, **13**, 995 (1965).

stereochemistry of this reduction, therefore, seems to be governed by Cram's cyclic model.[3]

The same reaction condition applied to the optically active ketone (IX) afforded N-benzoyl-*l*-norephedrine (X), m.p. 167~168°, $[\alpha]_D^{22}$ +40.0° (EtOH), and the hydrolysis of X with alkali gave the objective *l*-norephedrine, isolated as its hydrochloride (XI), m.p. 169.5~170.5°, $[\alpha]_D^{25}$ −30.6° (H_2O).

By consideration of the specific rotation of the starting material and that of the product, it is clear that no racemization occurred throughout the whole route of the present synthesis.

Experimental[*5]

(*R*)-2-Amino-3-phenyl-1-propanol (IV)——D-Phenylalanine, $[\alpha]_D^{24}$ +31.6° (c=1.088, H_2O), was esterified and reduced with $NaBH_4$[1,2] to afford IV as colorless needles of m.p. 93~94°. $[\alpha]_D^{22}$ +27.0° (c=1.316, EtOH). *Anal.* Calcd. for $C_9H_{13}ON$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.68; H, 8.53; N, 9.10.

(*R*)-N-(α-Hydroxymethylphenethyl)benzamide (V)——A mixture of IV (15.5 g., 0.103 mole) and BzCl (29.0 g., 0.206 mole) in pyridine (100 ml.) was allowed to stand at room temperature overnight. The pyridine was evaporated *in vacuo* and the residue was poured into ice-water. The deposited crystals were collected by filtration, dissolved in EtOH (400 ml.) containing NaOH (4.0 g., 0.10 mole) and the whole was refluxed for 1 hr. Evaporation of the solvent *in vacuo* gave a residue, which was diluted with ice-cold water. The insoluble solid was collected and recrystallized from EtOH to afford V (20.5 g., 78% yield), as colorless plates of m.p. 171~172° (reported m.p. 169°[4]), $[\alpha]_D^{25}$ +77.3° (c=0.356, EtOH). IR ν_{max}^{KBr} cm^{-1}: 1637, 1530~1520 (amide). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.21; H, 6.73; N, 5.32.

(*R*)-N-(α-Chloromethylphenethyl)benzamide (VI)——To $SOCl_2$ (25.0 g., 0.21 mole) was added V (16.5 g., 0.065 mole) directly at room temperature and, after the foaming ceased, the whole was heated on a water-bath for 5 min. Evaporation of excess $SOCl_2$ *in vacuo* gave a solid, which was recrystallized from a mixture of AcOEt-hexane to afford VI (16.5 g., 93% yield) as colorless needles of m.p. 132~134°, $[\alpha]_D^{24}$ +55.6° (c=0.716, EtOH). IR ν_{max}^{KBr} cm^{-1}: 3330 (NH), 1640, ~1535 (amide). *Anal.* Calcd. for $C_{16}H_{16}ONCl$: C, 70.19; H, 5.89; N, 5.11. Found: C, 70.04; H, 5.95; N, 5.24.

(*R*)-2-(2-Benzamido-3-phenylpropyl)-2-thiopseudourea Hydrochloride (VII)——A solution of VI (16.8 g., 0.062 mole) and thiourea (4.7 g., 0.062 mole) in EtOH (200 ml.) was refluxed for 1 hr. and then evaporated *in vacuo* to dryness. The residue was recrystallized from EtOH to afford VII (18.0 g., 84% yield) as colorless needles of m.p. 187~189°. *Anal.* Calcd. for $C_{17}H_{19}ON_3S \cdot HCl$: C, 58.35; H, 5.76; N, 12.01. Found: C, 58.35; H, 5.89; N, 11.78.

(*S*)-N-(α-Methylphenethyl)benzamide (VIII)——A mixture of VII (7.5 g.) and Raney Ni (150 g.) in EtOH (500 ml.) was refluxed with vigorous stirring for 7.5 hr. and then filtered. The filtrate and hot EtOH washing were combined and evaporated *in vacuo* to dryness, the residue was dissolved in $CHCl_3$, and passed through a column of silica gel (15 g.). The fractions eluted with $CHCl_3$ were combined and evaporated to dryness *in vacuo* to give crystals, which were recrystallized from 50% aq. EtOH to afford VIII (4.0 g., 78% yield) as colorless leaflets of m.p. 155~157° (reported m.p. 159~160°,[5] 155~156°[6]), $[\alpha]_D^{25}$ +64.5° (c=0.524, EtOH) (reported[5] $[\alpha]_D^{15}$ +67° (EtOH)). IR ν_{max}^{KBr} cm^{-1}: 3345 (NH), 1628, ~1537 (amide). *Anal.* Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.52; H, 7.17; N, 5.78.

(*S*)-N-(α-Methylphenacyl)benzamide (IX)——A solution of VIII (960 mg., 4 mmoles) in AcOH (15 g.) and Ac_2O (30 g.) was cooled to 2° in an ice-bath. Chromium trioxide (1.20 g., 12 mmoles) was added at once to this solution and the whole was stirred in an ice-bath for 3.5 hr., and then allowed to stand at room temperature overnight. The reaction mixture was poured into ice-water and extracted thoroughly with $CHCl_3$. The $CHCl_3$ extracts were combined and washed with aq. $NaHCO_3$ solution, aq. $NaHSO_3$ solution, and H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the $CHCl_3$ gave a pale yellow oil (900 mg.) which was chromatographed over silica gel (90 g.), using a solvent system of benzene-EtOH (98.5:1.5). The initially eluted part (260 mg.) was recrystallized from a mixture of benzene-hexane to

*5 All melting points are not corrected. Infrared spectra were measured with a Koken DS-301 spectrophotometer and optical rotations were measured with a Yanagimoto photo-magnetic direct reading polarimeter Model OR-20.

3) D. J. Cram, K. R. Kopecky: J. Am. Chem. Soc., **81**, 2748 (1959).
4) J. H. Hunt, D. McHale: J. Chem. Soc., **1957**, 2073.
5) W. Leithe: Ber., **65**, 660 (1932).
6) J. Bernstein, K. A. Losee, C. I. Smith, B. Rubin: J. Am. Chem. Soc., **81**, 4433 (1959).

afford IX (240 mg., 28% yield based on the unrecovered starting material) as colorless needles of m.p. 105~106°, $[\alpha]_D^{21}$ +5.0°(c=1.400, EtOH). This sample showed a depression of melting point when admixed with the corresponding racemate (XII). IR ν_{max}^{KBr} cm^{-1}: 3315 (NH), 1694 (ketone), 1625, 1529~1523 (amide). *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.05; H, 6.10; N, 5.54.

Subsequent elution with the same solvent afforded 140 mg. of pure starting material (VIII).

N-Benzoyl-*dl*-norephedrine (XIII)——A solution of DL-N-(α-methylphenacyl)benzamide (XII)[7] (500 mg., 2 mmoles) (m.p. 104~106°, IR ν_{max}^{KBr} cm^{-1}: 3410 (NH), 1689 (ketone), 1648, ~1527 (amide). Reported m.p. 103°,[7] 104~105°[8]) and $NaBH_4$ (100 mg., 2.5 mmoles*[6]) in EtOH (60 ml.) was stirred at room temperature for 5.5 hr. The reaction mixture was adjusted to pH 3 with 10% aq. HCl, filtered, and the combined solution of the filtrate and EtOH washings was evaporated under a reduced pressure. The residue was recrystallized twice from EtOH-H_2O (1:2) to afford XIII (360 mg., 70% yield) as colorless needles of m.p. 143~144° (reported[9] m.p. 143~144°). IR ν_{max}^{KBr} cm^{-1}: 3370 (sh), 3305 (NH and OH), 1634, ~1538 (amide). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.26; H, 6.78; N, 5.43.

***dl*-Norephedrine (XIV)**——A solution of XIII (250 mg.) dissolved in 30% aq. KOH (24 ml.) and EtOH (8 ml.) was refluxed for 9 hr. After cool, the reaction mixture was extracted with benzene, and the combined benzene extracts were washed with satd. aq. NaCl solution, and dried over anhyd. Na_2SO_4. Evaporation to dryness *in vacuo* gave a residue (160 mg.) which was recrystallized twice from ether to give XIV as colorless leaflets of m.p. 100~101.5°(reported m.p. 104°,[9] m.p. 102~103°[10]). This sample was proved to be identical with the authentic *dl*-norephedrine by the comparison of their infrared spectra and the mixed melting point determination. *Anal.* Calcd. for $C_9H_{13}ON$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.56; H, 8.56; N, 9.30.

N-Benzoyl-*l*-norephedrine (X)——A solution of IX (340 mg., 1.34 mmoles) and $NaBH_4$ (60 mg., 1.5 mmoles*[6]) in EtOH (40 ml.) was stirred at room temperature for 3 hr. The reaction mixture was adjusted to pH 3 with 10% aq. HCl, filtered, and the combined solution of the filtrate and EtOH washings was evaporated under a reduced pressure. The residue was recrystallized from EtOH-H_2O (1:2) to give X (240 mg., 70% yield) as colorless needles of m.p. 167~168°, $[\alpha]_D^{22}$ +40.0°(c=1.126, EtOH). IR ν_{max}^{KBr} cm^{-1}: 3370 (sh), 3305 (NH and OH), 1634, ~1538 (amide). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.01; H, 6.51; N, 5.54.

***l*-Norephedrine Hydrochloride (XI)**——A solution of X (240 mg.) dissolved in 30% aq. KOH (24 ml.) and EtOH (8 ml.) was refluxed for 8 hr. After cool, the reaction mixture was extracted with benzene, and the combined benzene extracts were washed with satd. aq. NaCl solution, and dried over anhyd. Na_2SO_4. Evaporation of the solvent to dryness *in vacuo* gave a residue, which was dissolved in 10% aq. HCl (20 ml.) and some insoluble material was filtered off. The filtrate and H_2O washings were combined and evaporated to dryness *in vacuo* to afford a solid which was recrystallized from a mixture of EtOH-iso-Pr_2O to give XI (100 mg., 56% yield) as colorless plates of m.p. 169~170.5° (reported[9] m.p. 171~172°), $[\alpha]_D^{25}$ −30.6°(c=0.366, H_2O) (reported[9] $[\alpha]_D$ −33.3°(H_2O)). *Anal.* Calcd. for $C_9H_{14}ONCl$: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.79; H, 7.66; N, 7.35.

The authors express their gratitude to Dr. H. Nishimura, Dainippon Pharmaceutical Co., Ltd., for the donation of authentic samples of *dl*-norephedrine and *dl*-norephedrine hydrochloride, and also to Tanabe Seiyaku Co., Ltd. for the supply of D-phenylalanine. Thanks are also due to the Central Analysis Room of this Faculty for infrared spectral and microanalytical data.

Summary

Stereoselective synthesis of *l*-norephedrine hydrochloride (XI) was investigated starting from D-phenylalanine (D-I), by making use of the comparable configuration at the α-carbon in D-I with the asymmetric center bearing the amino group in XI. The synthetic route is shown in Chart 2.

(Received August 9, 1965)

*6 Calculated assuming that the purity of $NaBH_4$ is about 95%.

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8) G. H. Cleland, C. Niemann: J. Am. Chem. Soc., **71**, 841 (1949).
9) W. N. Nagai, S. Kanao: Ann., **470**, 157 (1929).
10) J. Wein: Acta Chim. Acad. Sci. Hung., **17**, 181 (1958).