104. Kentaro Okumura, Keishi Kotera, and Ichizo Inoue :
Synthetic Studies on 2-Pyrrolidinone Derivatives. II.
The Configuration of Stereoisomers of 1-Phenyl-
3-amino-5-methyl-2-pyrrolidinone.

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In the previous paper,¹⁾ two isomers of 1-phenyl-3-amino-5-methyl-2-pyrrolidinone have been explicitly proved to have a same skeletal structure by leading them to 1-phenyl-3-hydroxyimino-5-methyl-2-pyrrolidinone (I). The relative configuration of amino-group on C₃ and methyl-group on C₅ in these diastereoisomers were now determined.

According to Hückel, *et al.*²⁾ 1-methyl-2-hydroxyiminocyclopentanone gives *trans*-amine exclusively when reduced with sodium-abs. ethanol, whereas catalytic reduction yields *cis*-amine predominantly (contaminated with 28% *trans*-amine). Assuming that 1-phenyl-3-hydroxyimino-5-methyl-2-pyrrolidinone (I) shows the similar aptitude as 1-methyl-2-hydroxyiminocyclopentanone, we submitted this compound (I) to reduction using: i) Platinum dioxide in glacial acetic acid, ii) Raney nickel in ethanol and iii) Aluminum-mercury in moist tetrahydrofuran. The results obtained are tabulated below (Table I). As can be seen from this table, the method (i) gave only II b with low yield;

TABLE I. Reduction of 1-Phenyl-3-hydroxyimino-5-methyl-2-pyrrolidinone

Catalyst	Solv.	Temp. (°C)	Press. kg./cm ²	II a ^{a)} Yield (%)	II b ^{a)} Yield (%)	Total Yield (%)
1 PtO ₂	AcOH	50~60	ordinary		29.0	29.0
2 Raney Ni	EtOH	50~60	32	19.6	21.5	41.1
3 Al-Hg		20±3		33.8	19.6	53.4

a) Yield as amine-picrate.

the method (ii) gave the reduction product in a better yield, in which the compound (II b) exists in a slight abundance than II a, hence without definite stereospecificity, while the predominant product by the method (iii) was II a. These results suggest that II a is the *trans*, and II b is the *cis*-isomer.

Studies of ultraviolet and nuclear magnetic resonance spectra of the 3-hydroxy-compounds (III a, III b), prepared from II a, II b by diazotization, and of the 3-amino-compounds (II a, II b), fortunately gave a clue for the solution of the relative configuration.

The absorption maxima of the ultraviolet spectra of II b and III a (Chart 1) lie in higher frequency with less intensity than those of II a and III b respectively. From this fact may be drawn an assumption that the configurational difference between the

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1) Part I. K. Okumura, I. Inoue: This Bulletin, 12, 718 (1964).

2) W. Hückel, R. Kupka: Chem. Ber. 89, 1694 (1956).

diastereoisomers (II a, II b, III a, and III b) have a direct influence³⁾ upon the conformations of anilino-C-N bond. Therefore, considering the close similarities of the absorption maximum and intensity between 1-phenyl-3-amino-2-pyrrolidinone ($\lambda_{\text{max}}^{\text{EtOH}}$ 246 m μ (ϵ 13000)) and 1-phenyl-3-hydroxy-2-pyrrolidinone ($\lambda_{\text{max}}^{\text{EtOH}}$ 246 m μ (ϵ 13040)), the pair with a close absorption maximum and intensity may be regarded to have the same configuration.

Fig. 1. Nuclear Magnetic Resonance Spectra of 3-Amino- and 3-Hydroxy-1-phenyl-5-methyl-2-pyrrolidinone

The chemical shifts are expressed as τ values (p.p.m.) referred to tetramethylsilane used as internal reference.

In the nuclear magnetic resonance spectra (Fig. 1), the signal of benzene ring proton of II b and III a, shows a singlet,⁴⁾ whereas, that of II a and III b multiplet. Two multiplet signals (τ , 7.2 and 8.2) of the methylene-protons of II b and III a, are separated by a range of 60~75 c.p.s., but that of II a and III b are closely associated. These spectrochemical results evidently indicate that each pair of II a, III b, and II b, III a, has the same configuration respectively, and give a clear cut evidence for the occurrence of Walden-inversion in the diazotization reaction of the amino-group on C₃ to give hydroxyl-group. In the pair of II a and III b, one proton of methylene which lies to same side with methyl group may be essentially deshielded by the long range magnetic anisotropy of the benzene ring located to an opposite direction from the methyl group. In the case of *cis* configuration, this proton exist also in same side with hydroxyl group, in which

3) G. H. Beaven : "Steric effects in conjugated system" ed. Gry Butterworths (London) (1958) p. 22.
 4) A. C. Huitric, *et al.* : J. Org. Chem., 28, 1539 (1963).

undergo the paramagnetic anisotropy of oxygen atom. As results, the large signal separation of methylene protons may be observed. But, in the *trans* configuration, two deshielding effects are shared with each proton of methylene group. Consequently, *cis* configuration at C₃ and C₅ of IIb and IIIa, can be deduced, which is also supported by synthesis as described below in Chart 2.

Chart 2.

Acetylation of *dl*-*allo*-hydroxyproline (IV) was carried out according to Gaudry's method⁵⁾ to give V, which, however, melted about 10° higher than that previously reported.⁵⁾ When V was hydrolyzed with 18% hydrochloric acid, there was recovered a single substance, which was proved to be identical with the starting *dl*-*allo*-hydroxyproline through direct comparison with an authentic sample by electrophoretic paper chromatography.⁶⁾ Thus the possible occurrence of epimerization during acetylation process was rendered improbable. V was then methylated with silver oxide and methyl iodide according to the method of Laurence⁷⁾ to give good yield of VI, which was hydrolyzed⁸⁾ first with aqueous solution of barium hydroxide, and then with dilute sulfuric acid, to yield *cis*-*dl*-4-methoxyproline (VII). The latter was reduced with lithium aluminum hydride after the Vogl's method⁹⁾ to give the pyrrolidinemethanol (VIII), the crude ditosylate (IX) of which was allowed to react with lithium aluminum hydride in absolute ether¹⁰⁾ to give the desired product (X), though in rather low yield (15%), as a colorless leaflets, m.p. 72~74°.

On the other hand IIIa was methylated as mentioned above and the resultant methyl ether (XI) was reduced with lithium aluminum hydride as usual. However, the yield of

- 5) R. Gaudry, C. Godin : J. Am. Chem. Soc., **76**, 139 (1954).
- 6) Th. Wieland, G. Pfeiderer : Angew. Chem., **69**, 200 (1957).
- 7) R. Laurence, M. Synge : Biochem. J., **33**, 1931 (1939).
- 8) A. Neuberger : J. Chem. Soc., **1945**, 429.
- 9) O. Vogl, M. Pöhm : Monatsh., **83**, 541 (1952).
- 10) P. Karrer, P. Dinkel : Helv. Chim. Acta, **36**, 122 (1953).

the product was so low that the method, modified by Shamma,¹¹⁾ was employed, which proved effective giving a fairly good yield (78%) of XIII. The elimination of phenyl-group from XIII was successfully carried out by the method of Braun-Muller¹²⁾ known as the common preparative method of secondary-amine. Tosylate (X) of the pyrrolidine (XIII) was easily obtained as a colorless leaflets, m.p. 75~75.5°, which was proved to be identical with X obtained before by mixed melting point test, analysis, and infrared spectrum. Thus *cis* configuration of IIIa was confirmed, consequently giving a proof for *trans* configuration of IIIb and IIa, and *cis* configuration of IIb.

Experimental

Reduction of 1-Phenyl-3-hydroxyimino-5-methyl-2-pyrrolidinone (I)—a) Catalytic reduction with PtO₂: A mixture of 0.3 g. (1.47 mmoles) of I in 10 ml. of AcOH and 50 mg. of PtO₂·H₂O was shaken in an atmosphere of H₂ at 50~60°. After absorption of one mole of H₂, the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in a few milliliter of 5% HCl and the solution was washed with CHCl₃, then made alkaline with K₂CO₃. Extraction and subsequent treatment in usual manner afforded the crude oil, to which an equimolar picric acid in a few milliliter of EtOH was added. The yellow picrate was recrystallized from EtOH to give only 0.176 g. (29% yield) of IIb·picrate, m.p. 187~188°. *Anal.* Calcd. for C₁₁H₁₄ON₂·C₆H₃O₇N₃: C, 48.69; H, 4.09; N, 16.69. Found: C, 49.04; H, 4.38; N, 16.79.

b) Catalytic reduction with Raney Ni: A mixture of 0.5 g. (2.45 mmoles) of I in 50 ml. of EtOH and 5 ml. of Raney Ni suspended in EtOH was shaken in an atmosphere of H₂ at 50~70° under pressure of 32 kg./cm² reaction mixture was worked up as described above and the precipitated crude picrate was recrystallized from 60% EtOH to give 0.2 g. (19.6% yield) of IIa·picrate in yellow needles, m.p. 217~219° (decomp.). The mother liquor was evaporated *in vacuo* and the residue was crystallized from EtOH to give 0.22 g. (21.5% yield) of IIb·picrate in yellow rhombs, m.p. 187~188° (decomp.). *Anal.* Calcd. for C₁₁H₁₄ON₂·C₆H₃O₇N₃: C, 48.69; H, 4.09; N, 16.69. Found: for IIa·picrate: C, 48.23; H, 3.73; N, 16.46.

c) Reduction with Al-Hg: A solution of 0.5 g. (2.45 mmoles) of I in 50 ml. of tetrahydrofuran containing 1 ml. of H₂O was stirred at a room temperature for 16 hr. with large excess of Al-Hg. The inorganic precipitates were removed by decantation and the solution was evaporated, and subsequent treatment of the residue with picric acid as described above afforded 0.385 g. (33.8% yield) of IIa·picrate, m.p. 215~218° (decomp.) and 0.2 g. (19.6% yield) of IIb·picrate, m.p. 185~188° (decomp.), which were respectively identical with authentic samples.

a) 1-Phenyl-3-hydroxy-5-methyl-2-pyrrolidinone (IIIa)—To a solution of 11.0 g. (0.058 mole) of IIa and 10 g. (0.087 mole) of 85% H₃PO₄ in 110 ml. of H₂O was added dropwise a solution of 4.85 g. (0.07 mole) of NaNO₂ in 52 ml. of H₂O at 0~-2° during 1.5 hr. with stirring. The mixture was stirred for an additional hour at the same temperature, then allowed to stand overnight at a room temperature. The product was extracted with CHCl₃ and the extract was washed with 5% HCl, satd. NaHCO₃ solution, H₂O and dried over anhyd. Na₂SO₄, evaporated. The residue was recrystallized from diisopropyl ether to give 5.6 g. (51% yield) of IIIa in colorless plates, m.p. 108~109.5°. *Anal.* Calcd. for C₁₁H₁₃O₂N: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.24; H, 6.69; N, 7.40.

b) 1-Phenyl-3-hydroxy-5-methyl-2-pyrrolidinone (IIIb)—To a solution of 5.8 g. (0.0305 mole) of IIb and 5.2 g. (0.0455 mole) of 85% H₃PO₄ in 60 ml. of H₂O was added dropwise a solution of 3.15 g. (0.0455 mole) of NaNO₂ in 30 ml. of H₂O at 0~-2° during 1.5 hr. with stirring. The mixture was stirred for an additional hour at the same temperature, then allowed to stand overnight at a room temperature, worked up as described above to give 2.8 g. (48% yield) of IIIb in colorless needles from benzene, m.p. 108~110°. *Anal.* Calcd. for C₁₁H₁₃O₂N: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.07; H, 6.77; N, 7.39.

Methyl *cis*-1-Acetyl-4-methoxy-2-pyrrolidinecarboxylate (VI)—A suspension of 62 g. (0.358 mole) of V, 206 g. of Ag₂O and 252 g. of CH₃I in 700 ml. of Me₂CO was stirred at 30~35° for 6 hr. Then the reaction mixture was allowed to stand overnight at a room temperature. Inorganic precipitates were filtered off. The filtrate was evaporated and the residue was treated again with 125 g. of Ag₂O and 153 g. of CH₃I in 500 ml. of Me₂CO. The mixture was worked up as in the first treatment to give 65 g. (84% yield) of VI as oil, b.p._{0.7} 145~150°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1750, 1650, 1100. *Anal.* Calcd. for C₉H₁₅O₄N: N, 6.96. Found: N, 6.52.

11) M. Shamma, P. D. Rosenstock: J. Org. Chem., 26, 718 (1961).

12) R. Munch, G. T. Thannhauser, D. L. Cottle: J. Am. Chem. Soc., 68, 1297 (1946).

cis-4-Methoxy-2-pyrrolidinecarboxylic Acid (VII)—A suspension of 73 g. (0.365 mole) of VI in 3650 ml. of 0.33*N* Ba(OH)₂ was stirred at 18~22° for 4.5 hr. The reaction mixture was adjusted to pH 1.2 by addition of 20% H₂SO₄ and the precipitated BaSO₄ was removed by filtration. The filtrate was concentrated to 800 ml. under reduced pressure and the residual solution was allowed to reflux for 3 hr. with 520 ml. of 5*N* H₂SO₄. After cooling, 420 g. of Ba(OH)₂·8H₂O was added to adjust the solution to pH 3.4~4.0 and the precipitated BaSO₄ was removed by filtration. The filtrate was passed slowly through a column containing IRA-120 and the eluent with *N* NH₄OH was concentrated thoroughly *in vacuo* to give 44 g. of crude VII, crystallization of which from 900 ml. of MeOH afforded 38 g. (71.5% yield) of VII in colorless prisms, m.p. 212~214° (decomp.).

Rf; 0.37 (BuOH-AcOH-H₂O=12:3:5)

Rf; 0.86 (phenol-H₂O=4:1 containing 0.5% NH₄OH)

Anal. Calcd. for C₆H₁₁O₃N: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.29; H, 7.56; N, 9.40.

cis-4-Methoxy-2-pyrrolidinemethanol (VIII)—To a solution of 9.5 g. (0.25 mole) of LiAlH₄ in 200 ml. of abs. tetrahydrofuran was added portionwise 14.5 g. (0.1 mole) of VII at 20°. The mixture was refluxed for 6 hr. to which 18 ml. of H₂O was added dropwise with ice-cooling. The inorganic precipitates were removed by filtration and the cake was repeatedly extracted with hot MeOH. The combined organic layer was evaporated to leave colorless oil, which on distillation gave 10.1 g. (77% yield) of VIII, b.p.₃ 104~107°. The neutral oxalate in very hygroscopic colorless needles from iso-PrOH, m.p. 135~137°. *Anal.* Calcd. for C₁₂H₂₆O₄N₂·C₂H₂O₄: C, 47.71; H, 8.01; N, 7.95. Found: C, 47.89; H, 7.69; N, 8.10.

1-Phenyl-3-methoxy-5-methyl-2-pyrrolidinone (XI)—A solution of 5.5 g. (0.028 mole) of IIIa in 60 ml. of Me₂CO with 8.3 g. of Ag₂O and 10.2 g. of CH₃I was stirred at 27~34° for 2 hr. After removal of inorganic solids, the solution was concentrated under reduced pressure and the residue was again treated with same amounts of the reagents to 5.7 g. of crude XI, which on crystallization from isopropyl ether yielded 5.45 g. (95% yield) of XI in colorless long needles, m.p. 79~80°. *Anal.* Calcd. for C₁₂H₁₅O₂N: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.90; H, 7.31; N, 6.79.

1-Phenyl-2-methyl-4-methoxypyrrolidine (XII)—To the mixed hydride, prepared by introducing 3.05 g. (0.023 mole) of anhyd. granular AlCl₃ in 50 ml. of abs. Et₂O to 0.875 g. (0.023 mole) of LiAlH₄ suspended in 35 ml. of abs. Et₂O, was added portionwise 3.75 g. (0.0183 mole) of XI at such a rate as to cause gentle refluxing. The mixture was refluxed for 10 hr. with stirring. Then excess hydride was decomposed by the cautious addition of 10.7 ml. of H₂O at temperature below 5°. The precipitates were filtered off and washed well with Et₂O. The combined Et₂O layer was dried over anhyd. K₂CO₃ and evaporated. The distillation of the residue afforded 3.04 g. (87% yield) of XII as a colorless oil, b.p.₃ 105~107.5°. Picrate in yellow cues from AcOEt, m.p. 136~137°. *Anal.* Calcd. for C₁₂H₁₇ON·C₆H₃O₇N₃: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.17; H, 4.70; N, 13.30.

2-Methyl-4-methoxypyrrolidine (XIII)—To a solution of 0.95 g. (5.0 mmoles) of XII in 3.65 g. of conc. HCl and 3.7 g. of crushed ice was added dropwise a solution of 0.36 g. (5.2 mmoles) of NaNO₂ below -6° during 1 hr., and stirring was kept for additional 1 hr. at the same temperature. Then the mixture was adjusted to pH 8.6 by the addition of 19 ml. of 2*N* aq. Na₂CO₃. The nitroso-compound was extracted with Et₂O and the extract was dried over anhyd. K₂CO₃, evaporated. The residue suspended in 8.9 ml. of 26% aq. NaHSO₃ was warmed at 35° for 1 hr., at 75° further 15 min. After cooling, the reaction mixture was acidified with 5 ml. of conc. HCl, concentrated *in vacuo*. To the residual oil was added 7 ml. of 50% aq. NaOH and the solution was extracted with Et₂O. The extract was dried over KOH, evaporated, and distillation of the residue afforded 0.28 g. (49% yield) of XIII as a colorless oil, b.p. 135~137°. Picrolonate in yellow needles from EtOH, m.p. 208~210°. *Anal.* Calcd. for C₆H₁₃ON·C₁₀H₈N₄O₅: C, 50.65; H, 5.58; N, 18.46. Found: C, 50.59; H, 5.40; N, 18.29.

cis-1-Tosyl-2-methyl-4-methoxypyrrolidine (X)—a) Reduction of X with LiAlH₄: To a solution of 1.31 g. (0.1 mole) of VIII in 5 ml. of abs. pyridine was added 5.07 g. (0.027 mole) of tosyl chloride in 13 ml. of abs. pyridine under cooling and the mixture was allowed to stand in a refrigerator for 3 days, then warmed at 40° for 1 hr., diluted with 100 g. of crushed ice and 73 ml. of 10% HCl. The oily portion was extracted with AcOEt, and the extract was washed with 2% HCl, then aq. NaHCO₃, dried over anhyd. Na₂SO₄, concentrated under reduced pressure. The residue was dissolved in benzene and the solution was chromatographed over Al₂O₃, then was eluted with the solvent (benzene-EtOH=8:2). Evaporation of the eluent afforded 3.0 g. of crude X as a yellow oil which has no absorption band in O-H stretching vibration region of IR spectrum. This crude X 0.63 g. (1.44 mmoles) dissolved in 10 ml. of abs. Et₂O was added dropwise to a solution of 0.071 g. (1.87 mmoles) of LiAlH₄ in 10 ml. of abs. Et₂O at temperature below 5°, and the mixture was stirred at a room temperature for 30 min., further refluxed with stirring for 6 hr. After cooling, 0.325 ml. of H₂O was added to the reaction mixture and the precipitates were filtered off. The filtrate was dried over anhyd. Na₂SO₄, evaporated. Extraction with hexane from the residue and removal of solvent afforded 75 mg. of white crystals, m.p. 67~72°. Further recrystallization from cyclohexane afforded 58 mg. (15% yield) of X in leaflets, m.p. 72~74°. *Anal.* Calcd. for C₁₃H₁₉O₃NS: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.20; H, 7.06; N, 5.04.

b) By tosylation of XIII: To a solution of 0.15 g. (1.3 mmoles) of XIII in 2 ml. of abs. pyridine was added a solution of 0.3 g. (1.57 mmoles) of tosyl chloride in 2 ml. of abs. pyridine under cooling, and the mixture

was allowed to stand at a room temperature, then poured onto crushed ice. The aqueous solution was adjusted to pH 3.0 with 10% HCl and the product was extracted with AcOEt. The extract was dried over anhyd. Na_2SO_4 , evaporated, and the residue was crystallized from hexane to give 0.2 g. (57% yield) of X in colorless leaflets, m.p. $70\sim 73^\circ$. Analytical sample crystallized in colorless leaflets from cyclohexane, m.p. $75\sim 75.5^\circ$, unchanged by admixture with X prepared from VIII, and the IR spectra of both compounds were completely identical.

The authors are grateful to Prof. Emeritus S. Sugasawa of the University of Tokyo, the Director Dr. N. Sugimoto and Dr. S. Saito for their kind and helpful advice. They are also grateful to Miss Y. Hirokawa for ultraviolet spectral measurements, and to the members of Analysis Room of Tokyo Research Laboratory for elemental microanalyses.

Summary

The reductions of 1-phenyl-3-hydroxyimino-5-methyl-2-pyrrolidinone, using i) Platinum dioxide in glacial acetic acid, ii) Raney nickel in Ethanol, and iii) Aluminum mercury in moist tetrahydrofuran, were carried out to furnish two isomeric amines, designated as IIa and 1-phenyl-3-amino-5-methyl-2-pyrrolidinone (IIb). Quantitative ratios of these amines formed as regard to the reduction methods allowed us to assign *cis*-configuration to IIb and *trans*-configuration to IIa.

From the studies of ultraviolet and nuclear magnetic resonance spectra of the 3-hydroxy-compounds, 1-phenyl-3-hydroxy-5-methyl-2-pyrrolidinone (IIIa) and 1-phenyl-3-hydroxy-5-methyl-2-pyrrolidinone (IIIb), prepared from IIa and IIb respectively, the occurrence of Walden-inversion in the diazotization reaction was concluded. At the same time *cis*-configuration of IIb and IIIa was also predicted, which was supported by leading IIIa to *cis*-1-tosyl-2-methyl-4-methoxypyrrolidine (X) synthesized from *dl*-*allo*-hydroxyproline.

(Received February 14, 1964)