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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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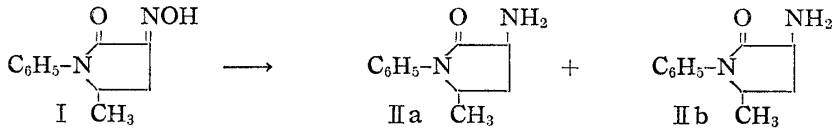
In the previous paper,[1] two isomers of 1-phenyl-3-amino-5-methyl-2-pyrrolidinone have been explicitly proved to have a same skeletal structure by leading them to 1-phenyl-3-hydroxyimino-5-methyl-2-pyrrolidinone (I). The relative configuration of amino-group on C_3 and methyl-group on C_5 in these diastereoisomers 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 IIb with low yield;

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



	Catalyst	Solv.	Temp. (°C)	Press. kg./cm²	IIa[a] Yield (%)	IIb[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 (IIb) exists in a slight abundance then IIa, hence without definite stereospecificity, while the predominant product by the method (iii) was IIa. These results suggest that IIa is the *trans*, and IIb is the *cis*-isomer.

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

The absorption maxima of the ultraviolet spectra of IIb and IIIa (Chart 1) lie in higher frequency with less intensity than those of IIa and IIIb 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).

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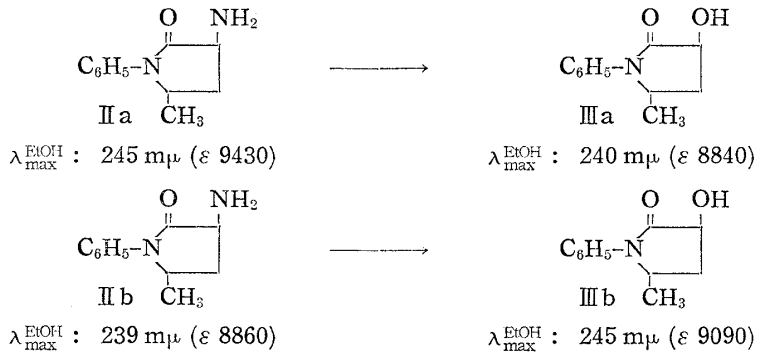

Chart 1. 1-Phenyl-3-hydroxy (and amino)-5-methyl-2-pyrrolidinones and their Absorption Maxima of Ultraviolet Spectra

diastereoisomers (IIa, IIb, IIIa, and IIIb) have a direct influence[3] 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 (λ_{max}^{EtOH} 246 mμ (ε 13000)) and 1-phenyl-3-hydroxy-2-pyrrolidinone (λ_{max}^{EtOH} 246 mμ (ε 13040)), the pair with a close absorption maximum and intensity may be regarded to have the same configuration.

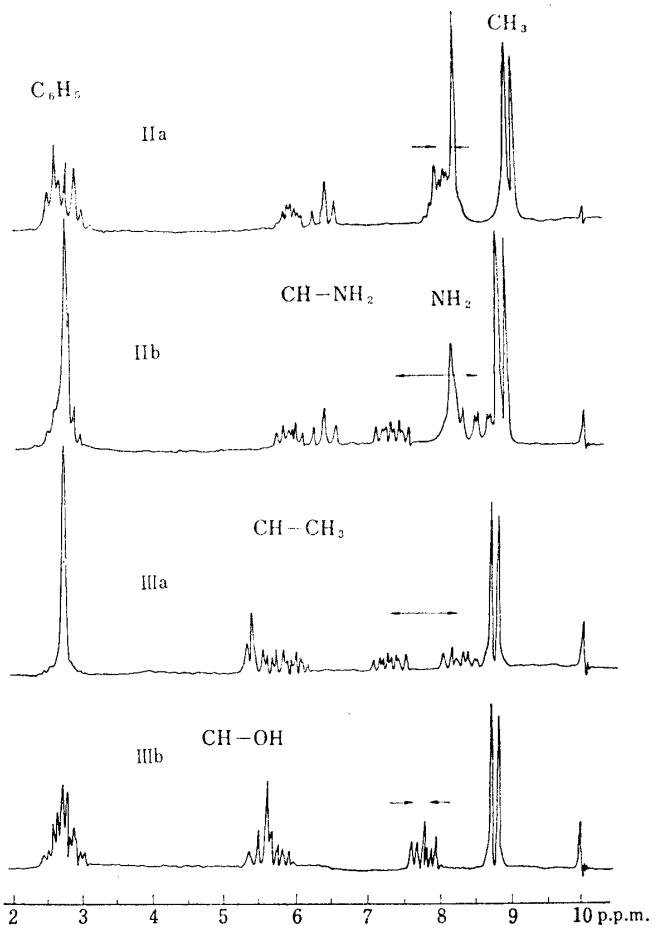

Fig. 1. Nuclear Magnetic Resonance Spectra of 3-Amino- and 3-Hydroxy-1-phenyl-5-methyl-2-pyrrolidinone

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 IIb and IIIa, shows a singlet,[4] whereas, that of IIa and IIIb multiplet. Two multiplet signals (τ, 7.2 and 8.2) of the methylene-protons of IIb and IIIa, are separated by a range of 60~75 c.p.s., but that of IIa and IIIb are closely associated. These spectrochemical results evidently indicate that each pair of IIa, IIIb, and IIb, IIIa, 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 C_3 to give hydroxyl-group. In the pair of IIa and IIIb, 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).

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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 C_3 and C_5 of IIb and IIIa, can be deduced, which is also supported by synthesis as described below in Chart 2.

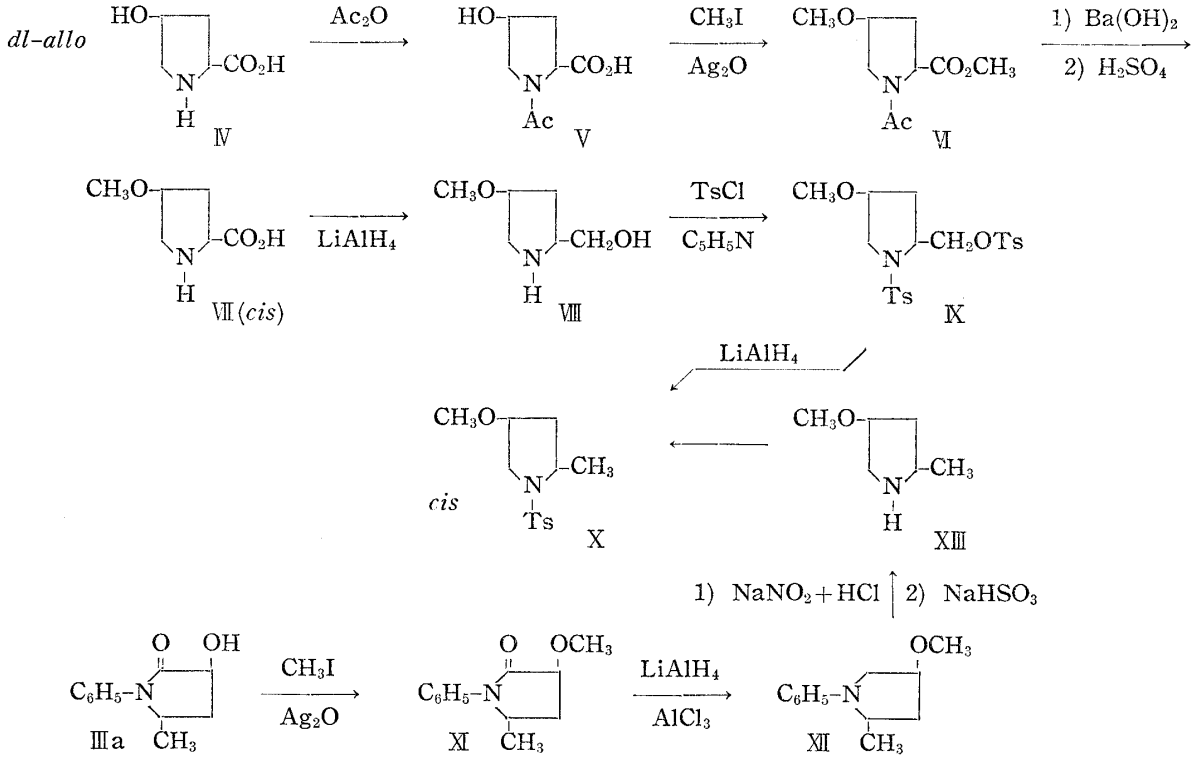

Chart 2.

Acetylation of *dl-allo*-hydroxyproline (IV) was carried out according to Gaudry's method[5] 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 Laurence[7] to give good yield of VI, which was hydrolyzed[8] 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 method[9] to give the pyrrolidinemethanol (VIII), the crude ditosylate (IX) of which was allowed to react with lithium aluminum hydride in absolute ether[10] 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. Pfleiderer : 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).

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the product was so low that the method, modified by Shamma,[11] was employed, which proved effective giving a fairly good yield (78%) of XII. The elimination of phenyl-group from XII was successfully carried out by the method of Braun-Muller[12] 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 PtO_2: A mixture of 0.3 g. (1.47 mmoles) of I in 10 ml. of AcOH and 50 mg. of $PtO_2 \cdot H_2O$ was shaken in an atmosphere of H_2 at 50~60°. After absorption of one mole of H_2, 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 $CHCl_3$, then made alkaline with K_2CO_3. 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 $C_{11}H_{14}ON_2 \cdot C_6H_3O_7N_3$: 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 H_2 at 50~70° under pressure of 32 kg./cm^2 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 $C_{11}H_{14}ON_2 \cdot C_6H_3O_7N_3$: 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 H_2O 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% H_3PO_4 in 110 ml. of H_2O was added dropwise a solution of 4.85 g. (0.07 mole) of $NaNO_2$ in 52 ml. of H_2O 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 $CHCl_3$ and the extract was washed with 5% HCl, satd. $NaHCO_3$ solution, H_2O and dried over anhyd. Na_2SO_4, 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 $C_{11}H_{13}O_2N$: 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% H_3PO_4 in 60 ml. of H_2O was added dropwise a solution of 3.15 g. (0.0455 mole) of $NaNO_2$ in 30 ml. of H_2O 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 $C_{11}H_{13}O_2N$: 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 Ag_2O and 252 g. of CH_3I in 700 ml. of Me_2CO 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 Ag_2O and 153 g. of CH_3I in 500 ml. of Me_2CO. 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 ν_{max}^{Nujol} cm^{-1}: 1750, 1650, 1100. *Anal.* Calcd. for $C_9H_{15}O_4N$: 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).

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***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% H_2SO_4 and the precipitated $BaSO_4$ 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* H_2SO_4. After cooling, 420 g. of $Ba(OH)_2 \cdot 8H_2O$ was added to adjust the solution to pH 3.4～4.0 and the precipitated $BaSO_4$ was removed by fiitration. The filtrate was passed slowly through a column containing IRA-120 and the eluent with *N* NH_4OH 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-H_2O=12:3:5)

Rf; 0.86 (phenol-H_2O=4:1 containing 0.5% NH_4OH)

Anal. Calcd. for $C_6H_{11}O_3N$: 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 $LiAlH_4$ 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 H_2O 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_8 104～107°. The neutral oxalate in very hygroscopic colorless needles from iso-PrOH, m.p. 135～137°. *Anal.* Calcd. for $C_{12}H_{26}O_4N_2 \cdot C_2H_2O_4$: 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 Me_2CO with 8.3 g. of Ag_2O and 10.2 g. of CH_3I 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 $C_{12}H_{15}O_2N$: 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 $AlCl_3$ in 50 ml. of abs. Et_2O to 0.875 g. (0.023 mole) of $LiAlH_4$ suspended in 35 ml. of abs. Et_2O, 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 H_2O at temperature below 5°. The precipitates were filtered off and washed well with Et_2O. The combined Et_2O layer was dried over anhyd. K_2CO_3 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 $C_{12}H_{17}ON \cdot C_6H_3O_7N_3$: 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 $NaNO_2$ 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. Na_2CO_3. The nitroso-compound was extracted with Et_2O and the extract was dried over anhyd. K_2CO_3, evaporated. The residue suspended in 8.9 ml. of 26% aq. $NaHSO_3$ 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 Et_2O. 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 $C_6H_{13}ON \cdot C_{10}H_8N_4O_5$: 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 Ⅸ with $LiAlH_4$: 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. $NaHCO_3$, dried over anhyd. Na_2SO_4, concentrated under reduced pressure. The residue was dissolved in benzene and the solution was chromatographed over Al_2O_3, then was eluted with the solvent (benzene-EtOH=8:2). Evaporation of the eluent afforded 3.0 g. of crude Ⅸ as a yellow oil which has no absorption band in O-H stretching vibration region of IR spectrum. This crude Ⅸ 0.63 g. (1.44 mmoles) dissolved in 10 ml. of abs. Et_2O was added dropwise to a solution of 0.071 g. (1.87 mmoles) of $LiAlH_4$ in 10 ml. of abs. Et_2O 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 H_2O was added to the reaction mixture and the precipitates were filtered off. The filtrate was dried over anhyd. Na_2SO_4, 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 $C_{13}H_{19}O_3NS$: 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

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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. 70~73°. Analytical sample crystallized in colorless leaflets from cyclohexane, m.p. 75~75.5°, unchanged by admixture with X prepared from Ⅷ, and the IR spectra of both compounds were completely identical.

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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.

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