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Catalytic Hydrogenation of Dimethylpyridine Methiodides and Stereochemistry of Hydrogenation Products[1]

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Catalytic hydrogenation of six kinds of N-methylpyridinium iodides gave pairs of geometrical isomers in a certain ratio for each methiodide. *ortho*-Dimethyl derivatives afforded almost exclusively *cis* isomers, *meta* derivatives gave *cis* isomers predominantly, and *para* derivative produced almost same amounts of both isomers. N-Methylpiperidines thus produced were quaternized with methyl iodide to N,N-dimethylpiperidinium iodides. The chemical shifts of equatorial and axial N-methyl protons were compared with each other, from which the substituent effects of α methyl groups was deduced. The results from nuclear magnetic resonance study enabled us completely to analyze the configurations and conformations of the hydrogenation products and their quaternary salts.

This paper concerns the stereochemistry of dimethylpiperidine (lupetidine) derivatives produced by catalytic hydrogenation of lutidine methiodides with Adams' platinum or Raney nickel. *cis*-and *trans*-isomers should be, in principle, produced from each lutidine methiodide with regard to the two C-methyl groups in the ring. In this paper, the configurations and, in addition, conformations of the hydrogenation products were systematically determined with a help of nuclear magnetic resonance (NMR) spectral analyses of the quaternary methiodides of the hydrogenation products.

Result and Discussion

Catalytic Hydrogenation of Dimethylpyridine Methiodides

Six kinds of dimethylpyridine methiodides were catalytically hydrogenated in two ways; with Adams' platinum in water and with Raney nickel (W-2)[3] in ethanol under atmospheric condition. The hydrogenation proceeded smoothly in almost all cases within a few to ten hours under the reaction conditions as described in the experimental part. In each case, two geometrical isomers, *cis* and *trans*, were produced with regard to the two C-methyl substituents, although production of the *cis* isomer was overwhelming preferred to the *trans* in 2,3- and 3,4-dimethyl derivatives. Their stereochemical structures were determined as described in the following part of this paper. The results are summarized in Table I.

The *cis*-and *trans*-isomers of the derivatives examined were separated by thin-layer chromatography (TLC), using alumina-G plates, or gas chromatography, the relative retention volumes and the *Rf* values being shown in Table II. The isomer which preceded the other on a gas chromatogram tended also to run faster on a thin-layer plate and vice versa. The *cis* and *trans*-isomers of 2,5-dimethyl derivative were separated easily by TLC but hardly by gas chromatography, and the 2,3-dimethyl isomers could, on the other hand, be separated only by gas chromatography. The preparative separation of the *cis*-and *trans*-isomers of 2,4-, 2,5-, 2,6-, and 3,5-dimethyl derivatives was readily achieved by alumina column chromatography.

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[1] This paper constitutes Part V of a series entitled "Stereochemistry in Solution." Part IV: M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **16**, 702 (1968).

[2] Location: *Tsukiji, Chuo-ku, Tokyo.*

[3] R. Mozingo, *Org. Synth.*, **21**, 15 (1941).

Table I. *cis–trans* Ratios of N-Methyl-dimethylpiperidines produced by Catalytic Hydrogenation of N-Methylpyridinium Iodides[a]

Starting material (Substituents)	Catalyst: Adams' Pt in H_2O *cis* (%)	Adams' Pt in H_2O *trans* (%)	Raney Ni in EtOH *cis* (%)	Raney Ni in EtOH *trans* (%)
2,3-Dimethyl	99	1	100	0
2,4-Dimethyl	96	4	96	4
2,5-Dimethyl[b]	65	35	27	73
2,6-Dimethyl	82	18	97	3
3,5-Dimethyl	82	18	70	30
3,4-Dimethyl	100	0	100	0

a) Hydrogenations were carried out under the atmospheric conditions.

b) These experimental values may include errors of about 3% due to analytical difficulty in gas chromatography.

Table II. Relative Retention Volumes in Gas Chromatography and Relative *Rf* Values in Thin-Layer Chromatography of N-Methylpiperidine Derivatives

N-Methylpiperidines (Substituents)	Relative retention volume[a]	Relative *Rf* value[b]
(N-Methylpiperidine)	1.00	1.00
cis-2,3-Dimethyl- [I]	1.78	1.2—1.3
trans-2,3-Dimethyl- [II]	1.63	1.2—1.3
cis-2,4-Dimethyl-[III]	1.40	1.58
trans-2,4-Dimethyl- [IV]	1.80	1.04
cis-2,5-Dimethyl- [V]	1.42[c]	1.82
trans-2,5-Dimethyl-[VI]	1.42[c]	2.27
cis-2,6-Dimethyl- [VII]	1.52	1.54
trans-2,6-Dimethyl- [VIII]	1.92	0.92
cis-3,5-Dimethyl- [IX]	1.34	2.47
trans-3,5-Dimethyl- [X]	1.22	2.95
cis-3,4-Dimethyl- [XI]	1.52	2.50

a) Retention volumes are referred to that of N-methylpiperidine. Gas chromatography was carried out with a glass column (4 mm × 1.8 m) of 30 % PEG-20M on Celite 545 (60—80 mesh) at a column temperature of 127°.

b) *Rf* values are referred to that of N-methylpiperidine. Chromatograms were obtained with Al_2O_3 glass plates eluted with ether.

c) These isomers were separable only by the temperature-programed gas chromatography (raised from 55° to 110° at a rate of 4°/min). The *cis* isomer had a larger retention volume than the *trans*.

The product ratio of the *cis*-and *trans*-isomers appears to depend on the relative position of the substituents, just as is known in a benzenoid system.[4] Thus, the *cis*-isomer overwhelmingly predominated over the corresponding *trans*-isomer in *ortho*-disubstituted derivatives; the *cis*-isomer was moderately predominant in *meta*-disubstituted derivatives; and both isomers were produced in comparable amounts in the *para*-isomers.

It is to be noted that the product ratio shown in Table I must be ruled mainly by kinetical control of the reaction concerned, because of independence of the duration of the reaction and the amount of catalyst. Furthermore, as will be reported in a forthcoming paper,[5] the

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4) J. Sauvage, R.H. Baker, and A.S. Hussey, *J. Am. Chem. Soc.*, **82**, 6090 (1960); S. Siegel and G.V. Smith, *ibid.*, **82**, 6082 and 6087 (1960); S. Siegel, G.V. Smith, B. Dmuchovsky, D. Dubbell, and W. Halpern, *ibid.*, **84**, 3136 (1962); R.D. Schuetz and L.R. Caswell, *J. Org. Chem.*, **27**, 486 (1962); S. Nishimura and H. Taguchi, *Bull. Chem. Soc. Japan*, **36**, 353 (1963); R.L. Burwell, *Chem. Rev.*, **57**, 905 (1957) and literatures cited therein.

5) Y. Kawazoe, M. Tsuda, and T. Horie, *Chem. Pharm. Bull.* (Tokyo), in press.

reaction rates for isomerization between *cis*-and *trans*-isomers under the reaction condition chosen in the present study are definitely too slow to bring about serious changes in *cis–trans* ratio of the products.

Assignments of *cis* and *trans* Isomers

The *cis–trans* assignment of 2,6-dimethylpiperidine derivatives has been conveniently achieved by NMR spectroscopy in two ways; one was based on the magnetic non-equivalent character of two benzyl–methylene protons of N-benzyl derivatives of the *trans*-isomer as described by Hill and Chan,[6] and the other was based on the magnetic equivalence of two N-methyl groups of quaternized N-methyl derivative of the *trans*-isomer, whereas the two N-methyls of the *cis*-isomer were magnetically non-equivalent as reported by us.[7] Alternatively, as demonstrated by Silhankova, *et al.*,[8] configurational analysis could be performed based on the temperature dependent changes in NMR spectra patterns of the *trans*-isomers of 1,2,4-, 1,2,6-, and 1,3,5-trimethylpiperidines. With regard to vicinally substituted dimethylpiperidines, 2,3- and 3,4-dimethyl derivatives, the *cis*-configuration may be assigned to the major product of catalytic hydrogenation of the corresponding aromatic amines. Silhankova, *et al.*[9] confirmed their configurations by isomerization of 2,3- and 3,4-dicarboxyl derivatives, followed by hydrogenation to the corresponding dimethyl derivatives. The assignment of the 2,3- dimethyl derivative is further supported by direct isomerization (energetical stabilization) of the major product to the other configurational isomer in the presence of platinum catalyst, as will be described in a forthcoming paper.[5] The *cis–trans* assignments for the 2,5-dimethyl derivative was made on the basis of an NMR study of the quaternary methiodide of this amine, as discussed in the following paragraph in this paper.

Conformational Analysis of N,N-Dimethylpiperidinium Iodides

In order to obtain an unequivocal evidence for configurational assignments of dimethylpiperidine derivatives, the conformations of N-methylpiperidinium iodides were taken into consideration, focusing attention on the magnetic shielding effect of C-methyl groups on the chemical shifts of N-methyl protons. Prior to the NMR measurements, the free energy difference of each conformer of these derivatives was estimated,[10] assuming that one *gausche* interaction between a substituent methyl group and the residual part of molecule is approximated to be 0.9 kcal/mole and 1,3-diaxial methyl-methyl interaction is an additional 1.9 kcal/mole.[11] The calculated values are shown in Table III.

Since the values shown here are estimated based on the assumption of the mathematical additivity of each steric interaction of groups using the values obtained from simple methylcyclohexanes, they may include considerable inaccuracy. They can, however, be considered to imply a measure for the stability–difference between two conformers. As shown in Table III, each two conformers of the *trans*-2,6- and *trans*-3,5-dimethyl derivatives are at the same energy level, respectively. It is, therefore, expected that two conformers of these derivatives are interconverting in solution quickly enough for the NMR time-scale at room temperature. In all other cases one conformer may be predominantly populated probably upto 90 to

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6) R.K. Hill and T.H. Chan, *Tetrahedron*, **21**, 2015 (1965).

7) Y. Kawazoe, M. Tsuda, and M. Ohnishi, *Chem. Pharm. Bull.* (Tokyo), **15**, 51 (1967).

8) A. Silhankova, D. Doskocilova, J. Beran, and M. Ferles, *Coll. Czech. Chem. Commun.*, 32, 3221 (1967).

9) A. Silhankova, D. Doskocilova, and M. Ferles, *Coll. Czech. Chem. Commun.*, **34**, 1976 (1969).

10) Possibility for existence of the boat–form conformation is excluded from the discussion of this paper. This may be reasonable assumption for almost all cases.

11) The energy level of 1,3-diaxally oriented dimethylcyclohexane is reported to be higher by 5.5 kcal/mole than that of the corresponding diequatorial conformer, hence the interaction between the two methyl substituents is assumed to be 1.9 kcal/mole in this paper.[12,13]

12) E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Co., New York, 1962, p. 214.

13) N.L. Allinger and M.A. Miller, *J. Am. Chem. Soc.*, **83**, 2145 (1961).

Table III. Conformational Energy Differences of N,N-Dimethyl-dimethylpiperidinium Salts

Substituents	Conformation	No. of interactions *gauche*	 1,3-dimethyl	Calculated interaction energy[a]
cis-2,3-Dimethyl [I]	2(e)3(a)	7	1	8.2 kcal/mole
	2(a)3(e)	6	0	5.4 kcal/mole
trans-2,3-Dimethyl [II]	2(e)3(e)	5	0	4.5 kcal/mole
	2(a)3(a)	7	1	8.2 kcal/mole
cis-2,4-dimethyl [III]	2(e)4(e)	4	0	3.6 kcal/mole
	2(a)4(a)	7	1	8.2 kcal/mole
trans-2,4-Dimethyl [IV]	2(e)4(a)	6	0	5.4 kcal/mole
	2(a)4(e)	5	0	4.5 kcal/mole
cis-2,5-Dimethyl [V]	2(e)5(a)	6	1	7.3 kcal/mole
	2(a)5(e)	5	0	4.5 kcal/mole
trans-2,5-Dimethyl [VI]	2(e)5(e)	4	0	3.6 kcal/mole
	2(a)5(a)	7	1	8.2 kcal/mole
cis-2,6-Dimethyl [VII]	2(e)6(e)	6	0	5.4 kcal/mole
	2(a)6(a)	8	1	9.1 kcal/mole
trans-2,6-Dimethyl [VIII]	2(e)6(a)	7	0	6.3 kcal/mole
	2(a)6(e)	7	0	6.3 kcal/mole
cis-3,5-Dimethyl [IX]	3(e)5(e)	2	0	1.8 kcal/mole
	3(a)5(a)	6	3	11.1 kcal/mole
trans-3,5-Dimethyl [X]	3(e)5(a)	4	1	5.5 kcal/mole
	3(a)5(e)	4	1	5.5 kcal/mole
cis-3,4-Dimethyl [XI]	3(e)4(a)	5	0	4.5 kcal/mole
	3(a)4(e)	5	1	6.4 kcal/mole
trans-3,4-Dimethyl [XII]	3(e)4(e)	3	0	2.7 kcal/mole
	3(a)4(a)	6	1	7.3 kcal/mole

a) Interaction energy calculated using values of 0.9 kcal/mole and 1.9 kcal/mole for a *gauche* interaction and a 1,3-diaxial methyl-methyl interaction, respectively.

100%.[14] It is worth emphasizing that the calculatons predict that, in the *cis*-2,3-, *trans*-2,4-, and *cis*-2,5-dimethyl derivatives, the methyl group at the α position is preferably oriented axially, hence the other methyl is equatorial.

The chemical shifts of these compounds were measured both in water and in chloroform, the results being shown in Table IV. The results indicate that neither a β- nor a γ-methyl group significantly changes the chemical shifts of the N-methyl protons. The substituent effects of α-methyl groups on the chemical shifts of N-methyl protons were tentatively deduced from the observed values shown in Table IV so as to be consistent with as much of the data as possible.[15] The equatorial and axial N-methyl protons in the parent compound of N,N-dimethylpiperidine were assumed to resonate at 3.117 and 3.050 ppm, respectively, from the reference dimethylsilapentasulfonate (DSS) signal in water and at 3.350 and 3.550 ppm, respectively, from the reference tetramethylsilane (TMS) signal in chloroform.[16] The effects of α-substituted C-methyl groups on the chemical shifts of N-methyl protons are shown in Chart 1.

The substituent effects presently obtained are qualitatively supported from the theoretical consideration of magnetic anisotropy of C–C bond.[19,20] It is to be noted that the effect of

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14) With regard to 2,4-dimethyl derivative, population-difference may not be so large but still exist to a considerable extent.

15) Values were roughly estimated, without any mathematical treatment such as the method of least squares.

16) These values are the observed values from β-methyl-N,N-dimethylpiperidine where β-methyl is held in an equatorial position almost exclusively.[17,18]

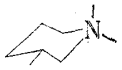
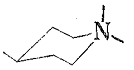
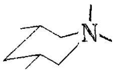
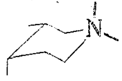
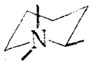
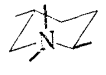
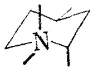
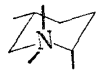
17) H.O. House, B.A. Tefertiller, and G.C. Pitt, *J. Org. Chem.*, **31**, 1073 (1966).

18) Y. Kawazoe and M. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **15**, 1405 (1967).

19) J.I. Musher, *J. Chem. Phys.*, **35**, 1159 (1961).

20) N. Muller and W.C. Tosch, *J. Chem. Phys.*, **37**, 1167 (1962).

Table IV. Observed Chemical Shifts of N-Methyl Protons of Methyl-substituted N,N-Dimethylpiperidines Dissolved in Water and Chloroform and Calculated Values on the Basis of the Estimated Substituent Effects of Methyl Groups in α-Position[a]

N,N-Dimethyl piperidinium iodides	Chemical shifts of N-methyl protons[b]					
	Equatorial N-methyl			Axial N-methyl		
	obs.	calc.	Δδ (ppm)[c]	obs.	calc.	Δδ (ppm)[c]
Non-substituted						
	3.117 (3.550	3.117 3.550	0.000 0.000)	3.050 (3.350	3.050 3.350	0.000 0.000)
	3.117 (3.550	3.171 3.550	0.000 0.000)	3.050 (3.317	3.050 3.350	0.000 +0.033)
	3.142 (3.550	3.117 3.550	−0.025 0.000)	3.083 (3.375	3.050 3.350	−0.033 −0.025)
	3.142 (insoluble)	3.117	−0.025	3.083 (insoluble)	3.050	−0.033
α-Equatorial methyl-						
	3.067 (3.450	3.100 3.475	+0.033 +0.025)	2.883 (3.150	2.917 3.150	+0.034 0.000)
	3.133 (3.467	3.100 3.475	−0.033 +0.008)	2.950 (3.167	2.917 3.150	−0.033 −0.017)
	3.133 (3.508	3.100 3.475	−0.033 −0.033)	2.967 (3.142	2.917 3.150	−0.050 +0.008)
	3.083 (3.475	3.100 3.475	+0.017 0.000)	2.917 (3.175	2.917 3.150	0.000 −0.025)
	3.050 (3.367	3.083 3.400	+0.033 +0.033)	2.758 (2.925	2.783 2.950	+0.025 +0.025)
α-Axial methyl-						
	3.067 (3.408	3.033 3.367	−0.034 −0.041)	3.217 (3.567	3.200 3.567	−0.017 0.000)
	3.017 (3.317	3.033 3.367	+0.016 +0.050)	3.183 (3.575	3.200 3.567	+0.017 −0.008)
	3.008 (3.400	3.033 3.367	+0.025 −0.033)	3.175 (3.567	3.200 3.567	+0.025 0.000)

a) NMR spectra were measured at 20°.

b) Values in parentheses indicate the chemical shifts observed in chlroform. Chemical shifts are shown in ppm unit referred to the standard signal of sodium dimethylsilapentasulfonate (DSS) in water and to that of tetramethylsilane in chloroform.

c) Deviations of the observed chemical shifts from the calculated ones.

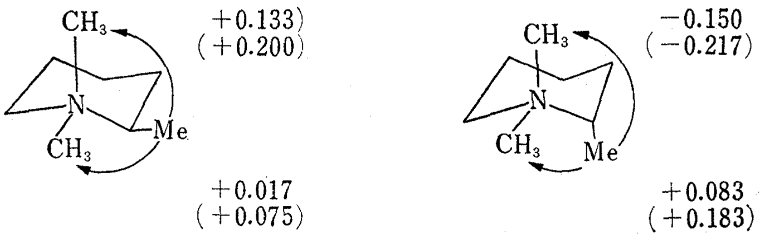


Chart 1

Substituent effects in ppm of α-C-methyl group on the chemical shifts of axial and equatorial N-methyl protons in water and chloroform (Values in parentheses indicate the effect in chloroform).

an α-equatorial methyl group on the axial N-methyl protons is remarkably larger than the effect on equatorial ones, although the gauche relation would be expected between the methyl groups concerned in either case. The same type of inequality was described for the substituent effect of an equatorial C-methyl group on the chemical shift of ring methylene protons of methylcyclohexanes.21) It is also worth noting that one can find much larger effects of α-C-methyl group in chloroform than those in water, suggesting that there may probably be a remarkable difference in the sterochemistry around the quaternary ring nitrogen.

It is safely concluded, apart from the interesting features of NMR spectra of these compounds, that reliability in assignments of *cis–trans* relationship made in the present study is strongly supported by the fact that all the chemical shift data of N-methyl protons were coincided well with the values calculated with the above substituent effects. It is of interest to note that the higher field methyl signal was assigned to the equatorial N-methyl protons for *cis*-2,3-, *trans*-2,4-, and *cis*-2,5-dimethyl derivatives which were predicted to have an axial methyl group at the α-position, whereas the reverse assignments were made in all other compounds as in general.17,18)

Experimental

Purification of Lutidines——Six kinds of lutidines purchased from Tokyo Kasei Co. (Tokyo) were purified by recrystallization of their hydrochlorides or picrates from a suitable solvent (MeOH, EtOH, or isopropanol). The purity was confirmed to be sufficient for the present study (99%).

Preparation of Lutidinium Methiodides——After 10 ml of methyliodide was added to 5 g of lutidine in 40 ml of acetone, the reaction mixture was refluxed for 3 hr. The solvent was evaporated *in vacuo*. The resulting crystalline residue was washed twice with 50 ml of ether and recrystallized from MeOH, EtOH, or isopropanol. The melting points and crystal forms of the products are shown in Table V.

TABLE V. Lutidinium Methiodides

Pyridinium methiodides	Crystal form	Melting point (°C)
2,3-Dimethyl-	white prism	204.5—206 (EtOH)[a]
2,4-Dimethyl-	white needle	115—117.5 (isopropanol)
2,5-Dimethyl-	white needle	177—178 (EtOH)
2,6-Dimethyl-	white needle	236—237 (MeOH)
3,5-Dimethyl-	white prism	271—272 (EtOH)
3,4-Dimethyl-	white needle	117—119 (EtOH)

a) Solvents in parentheses indicate the recrystallization solvent.

Hydrogenation of 2,3-Lutidinium Methiodide with Platinum——Five grams of 2,3-lutidinium methiodide dissolved in 30 ml of H_2O was hydrogenated in the presence of 300 mg of Adams' platinum under the atmospheric condition. Hydrogen-uptake was completed during about 7 hr. After removal of the catalyst by filtration and the solvent by evaporation *in vacuo*, the resulting hydroiodide of the reduction product was freed from the acid residue by addition of conc. aqueous NaOH into the free base, which was extracted with ether. Evaporation of the solvent yielded about 2.0 g of *cis*-1,2,3-trimethylpiperidine (I). The product was confirmed to be almost pure *cis*-isomer (*ca.* 99%) without further purification by gas chromatography.

Preparation of *trans*-1,2,3-Trimethylpiperidine (II) by Isomerization of the *cis*-Isomer with Platinum——The solution of 260 mg of *cis*-1,2,3-trimethylpiperidine (I) hydrochloride in 15 ml of H_2O was stirred in the presence of 600 mg of Adams' platinum in hydrogen gas atmosphere at room temperature for 48 hr. The reaction mixture was filtered and the filtrate was evaporated to dryness. The recovered material was made alkaline with a small amount of conc. NaOH aq. to liberate the free amines, which were extracted with ether. The etheral layer was dried over anhyd. Na_2SO_4. The gas chromatogram of the ether extract of amines showed a newly generated peak, which came out prior to the original *cis* peak. The former was

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21) A. Segre and J.I. Musher, *J. Am. Chem. Soc.*, **89**, 706 (1967).

assigned to the *trans*-isomer (II). The *cis–trans* ratio was proved to be 35:65 by gas chromatography. These *cis*-and *trans*-isomers could not be separated from each other by neither TLC nor recrystallization of the picrates.

Hydrogenation of 2,4-Lutidinium Methiodide with Platinum——Hydrogenation of 2,4-lutidinium methiodide was carried out, as in the case of 2,3-lutidinium methiodide, to yield 2.0 g of a mixture of *cis*-and *trans*-1,2,4-trimethylpiperidines (III and IV). The *cis-trans* ratio of the product was determined to be 96:4 by gas chromatography. The separation of the geometrical isomers was readily carried out by Al_2O_3 column chromatography eluting with ether. The *cis*-isomer was eluted first and then the trans one came out. The melting points of picrates of the *cis*-and *trans*-isomers (III and IV) were 172—173° and 199—201°, respectively.

Table VI. Melting Points of Methiodides and Picrates of N-Methyl-dimethylpiperidines

N-Methylpiperidines	Melting point	
	Methiodide	Picrate
cis-2,3-Dimethyl- [I]	283—285 (EtOH)a)	218—222 (EtOH)a)
trans-2,3-Dimethyl- [II]	—	—
cis-2,4-Dimethyl- [III]b)	273—276 (EtOH)	172—173 (EtOH)
trans-2,4-Dimethyl- [IV]b)	—	199—201 (isoprop.)
cis-2,5-Dimethyl- [V]	280—282 (EtOH)	184—186 (EtOH)
trans-2,5-Dimethyl- [VI]	258—261 (EtOH)	179—180 (EtOH)
cis-2,6-Dimethyl- [VII]c–e)	280—282 (EtOH)	225—227 (EtOH)
trans-2,6-Dimethyl- [VIII]	300—301 (EtOH)	244—245 (EtOH)
cis-3,5-Dimethyl- [IX]b)	275—276 (EtOH)	147—148 (EtOH)
trans-3,5-Dimethyl- [X]b)	236—238 (EtOH)	149—150 (EtOH)
cis-3,4-Dimethyl- [XI]	278—281 (EtOH)	202—204 (MeOH)

a) The solvent used for recrystallization is shown in paretheses.
b) A. Silhankova, D. Doskocilova J. Beran, and M. Ferles, *Colletct. Czech. Chem. Commun.*, **32**, 3221 (1967)
c) N. J. Leonard and F.D. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957)
d) Y. Kawazoe, M. Tsuda, and M. Ohnishi, *Chem. Pharm. Bull.* (Tokyo), **15**, 56 (1967)
e) R. Lukes and J. Jizba, *Chem. Lisy*, **46**, 622 (1952) (*Chem. Abstr.*, **47**, 9325 (1953))

Hydrogenation of 2,5-Lutidinium Methiodide with Platinum——2,5-Lutidinium methiodide was hydrogenated in a similar manner to the case of 2,3-lutidinium methiodide to yield a mixture of *cis*-and *trans*-1,2,5-trimethylpiperidines (V and VI, respectively). The *cis–trans* ratio of the product was determined to be 65:35 by gas chromatography. The separation of the *cis*-and *trans*-isomers was carried out by Al_2O_3 column chromatography eluting with ether. The careful fractionation gave pure *trans*-isomer (VI) in an earlier part of eluate and then pure *cis* isomer (V) in the following part. The yield of the *cis*-and *trans*-isomers were 63 and 37%, respectively. The *cis*-isomer gave yellow plates picrate, mp 184—186°, and the *trans*-one gave yellow stick picrate, mp 179—180°.

Hydrogenation of 2,6-Lutidinium Methiodide with Platinum——2,6-Lutidinium methiodide was hydrogenated in the same manner as the cases of other lutidine isomers to afford a mixture of *cis*-and *trans*-1,2,6-trimethylpiperidines. The *cis–trans* ratio of the product was determined to be 82:18 by gas chromatography. The separation of *cis*-and *trans*-isomers (VII and VIII, respectively) was carried out effectively by Al_2O_3 column chromatography eluting with ether. The *cis* isomer was eluted first and then the *trans*-one came out. The yield was almost quantitatively. The melting points of the picrates of the *cis*-and *trans*-isomers were 225—227° and 244—245° (decomp.), respectively.

Hydrogenation of 3,5-Lutidinium Methiodide with Platinum——3,5-Lutidinium methiodide was treated in the same manner as the above to yield a mixture of *cis*-and *trans*-1,3,5-trimethylpiperidines (IX and X, respectively). The *cis–trans* ratio of the product was determined to be 82:18 by gas chromatography. The separation of the isomers was carried out by Al_2O_3 column chromatography eluting with ether. The *trans*-isomer was eluted first and then *cis*-one came out. The melting points of the picrates of the *cis*-and *trans*-isomers were 147—148° and 149—150°, respectively.

Hydrogenation of 3,4-Lutidinium Methiodide with Platinum——3,4-Lutidinium methiodide was hydrogenated in the same manner as the above to afford pure *cis*-1,3,4-trimethylpiperidine (XI) in almost quantitative yield. Its picrate melt at 202—204°.

General Procedure for Hydrogenation of Lutidinium Methiodides with Raney Nickel——One gram of a lutidinium methiodide dissolved in 25 ml of EtOH was hydrogenated with 1 ml (wet volume) of Raney nickel (W-2) under the atmospheric condition. After hydrogen absorption was completed, the nickel catalyst was removed by filtration. The filtrate was acidified with conc. HCl and then evaporated to dryness. The reduction product was once isolated as the salt, from which the free base was liberated by addition of conc. NaOH aq. solution and extracted with ether. The ether extract of amines was analyzed by gas chromatography for determination of the *cis–trans* ratio of the isomers produced.

Quaternization of Trimethylpiperidines with Methyliodide——Quaternization was carried out by refluxing the acetone solution (30 ml) of 250 mg of a trimethylpiperidine with 1 ml of MeI for 1 hr. After evaporation of the solvent, the resulting white crystalline material was recrystallized from a suitable solvent (MeOH, EtOH, or isopropanol) as shown in Table VI.

Nuclear Magnetic Resonance Measurements——NMR spectra were obtained with a JNM-60-H spectrometer (Japan Electron Optics Laboratory, Tokyo), operating at 60 Mcps. The chemical shifts were measured in the signal-lock system with the internal standard, represented in the ppm unit from the signal position of tetramethylsilane in chloroform solutions and from that of sodium DSS in aqueous solutions.

Gas Chromatography——Gas chromatograms were obtained with a SHIMAZU GC-1B Gas Chromatograph with a hydrogen flame ionization detection system.

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