[Chem. Pharm. Bull. 19(2) 429—432 (1971)] UDC 547.822.3.04 : 546.92.04

Studies on Hydrogen Exchange. XI.[1] Isomerization of *cis* and *trans* Isomers of Alkylpiperidines catalyzed by Adams' Platinum

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(Received September 7, 1970)

When dimethylpyridine methiodides are hydrogenated to dimethylpiperidines, a pair of *cis* and *trans* isomers is produced with regard to the two C-methyl groups in each derivative.[3] This paper concerns the epimerization of the C-methyl groups, *i.e.*, the *cis–trans* interconversion of dimethylpiperidine derivatives catalyzed by Adams' platinum. The *cis–trans* isomerization will be discussed in connection with the hydrogen exchange of the CH function bearing the methyl group concerned. Although some successful results have already been reported on the hydrogen exchange of aliphtic CH functions catalyzed by group VIII transition metals, no systematic studies have been found in literatures on aliphatic amines so far.

Result and Discussion

Dimethylpiperidine derivatives were prepared by catalytic hydrogenation of dimethylpyridine methiodides or hydrochlorides and separated into the *cis* and *trans* isomers by alumina column chromatography, when necessary.[3] Isomerization was carried out by stirring the aqueous solutions of the hydrochlorides of the amines to be examined in the presence of more than three molar equivalents of platinum catalyst which had been prepared by hydrogenation of platinum oxide. The reactions were performed at 30° under hydrogen atmosphere. For the hydrogen exchange study, the reaction was carried in deuterium oxide (D_2O) under

TABLE I. *cis–trans* Isomer–Ratios of Hydrogenation Products of Pyridines and Related Compounds and of Their Isomerization Products catalyzed by Platinum

Compound	Isomer–Ratio			
	Hydrogenation[a]		Isomerization[b]	
	cis (%)	*trans* (%)	*cis* (%)	*trans* (%)
2,6-Dimethylpiperidine	95	5	90	10
1,2,6-Trimethylpiperidine	82	18	65	35
1,2,3-Trimethylpiperidine	99	1	35	65
1-Methyldecahydroquinoline	60	40	30	70
1,3,5-Trimethylpiperidine	82	18	——[c]	
2-Methyldecahydroisoquinoline	90	10	——[c]	

a) Dimethylpyridine methiodides were catalytically hydrogenated in water at room temperature in the presence of Adams' Pt under an ordinary H_2 atmosphere.
b) Methylpiperidines were isomerized by Adams' Pt in water at room temperature under an ordinary H_2 atmosphere until the reaction reached to the equilibrium.
c) No isomerization was induced by platinum catalyst under the reaction condition chosen in the present study.

1) Part X: N. Uehara and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **18**, 203 (1970).
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3) M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **18**, 2499 (1970).

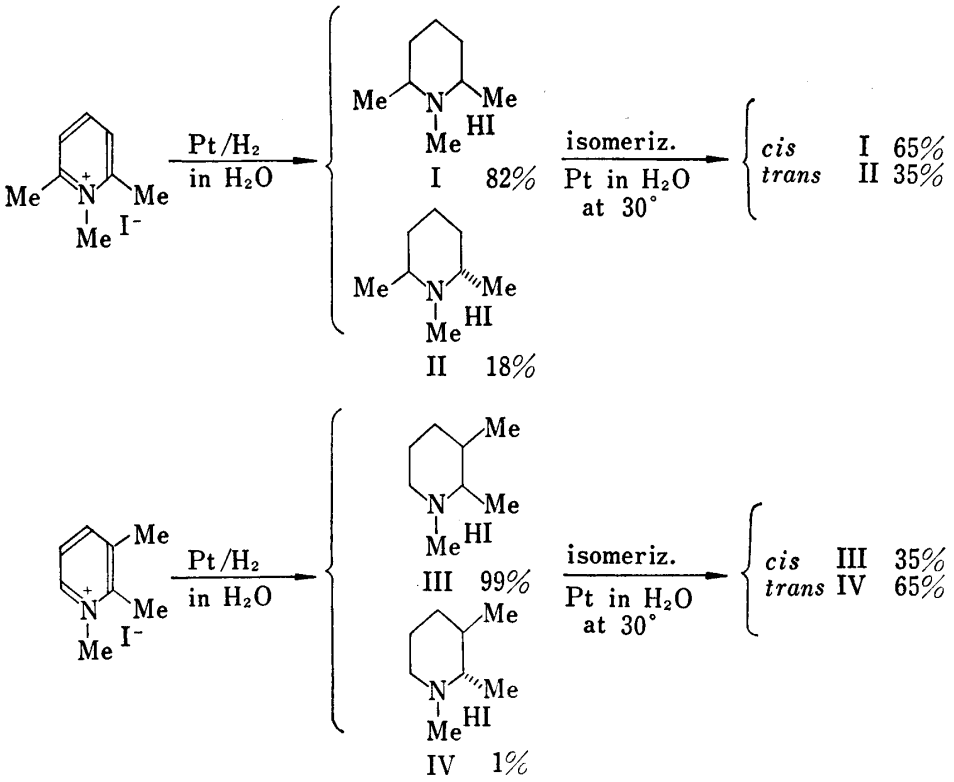


Chart 1

deuterium gas atmosphere instead of ordinary water and hydrogen gas. The *cis* and *trans* isomers of each derivative were quantitatively analyzed by nuclear magnetic resonance spectroscopy and/or gas chromatography.

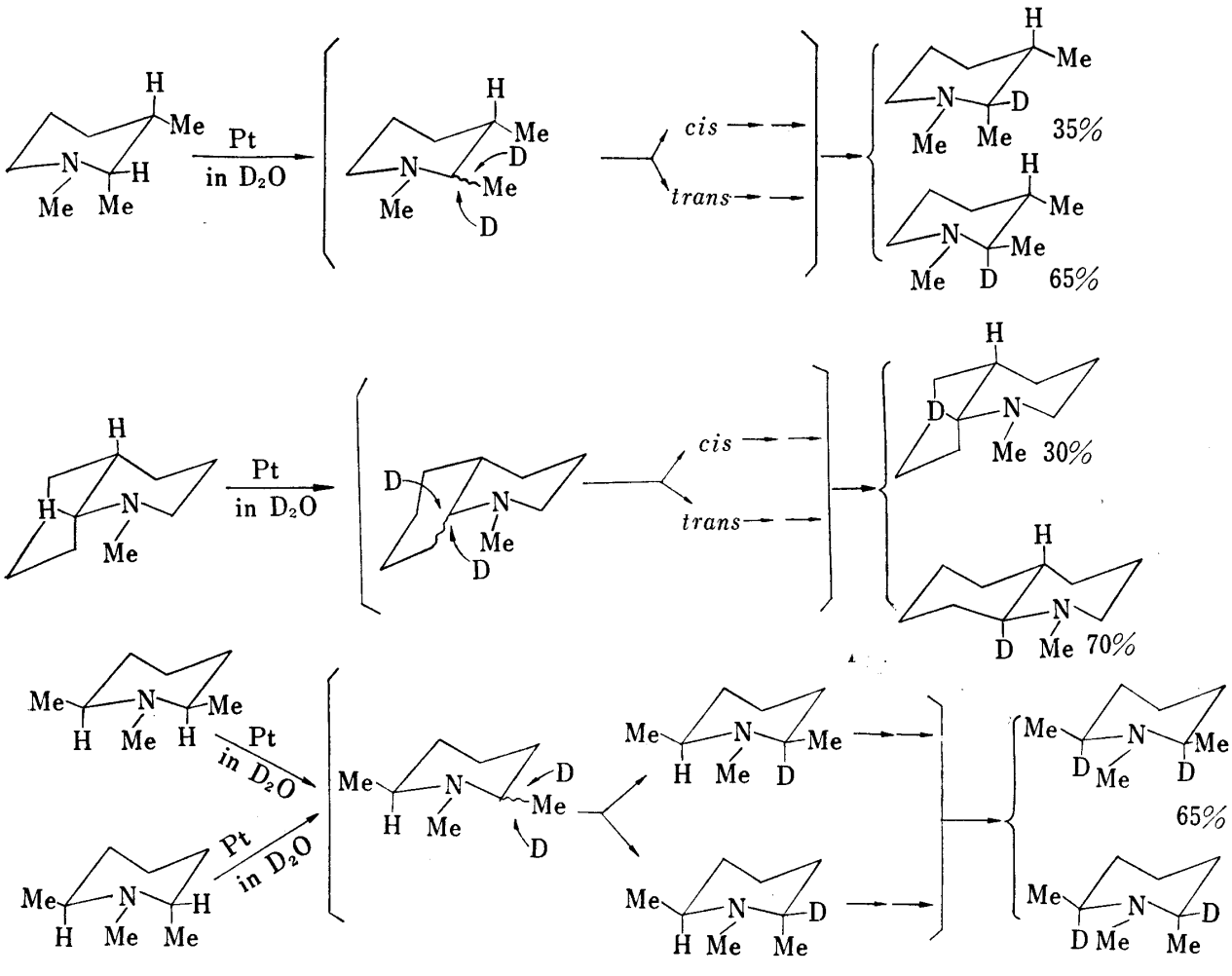
Table I shows the *cis–trans* ratios of the products equilibrated in the catalytic isomerization and also the ratios of the products in the catalytic hydrogenation of dimethylpyridines.[3] The isomer–ratios in the hydrogenation must be kinetically controlled, whereas the ratios in the catalytic isomerization may be considered to reflect the relative thermodynamic stability between the *cis* and *trans* isomers.[4] The free energy differences between *cis* and *trans* isomers may be evaluated, on this assumption, to be 0.37 and 1.32 kcal/mole at 30° for 1,2,6-trimethylpiperidine and 2,6-dimethylpiperidine, respectively.[5]

It is worth noting that, under the reaction conditions chosen in the present study, epimerization occurred only on α carbon atoms to the ring nitrogen. Thus, catalytic isomerization took place at room temperature of 1,2,3- and 1,2,6-trimethylpiperidines and 1-methyldecahydroquinoline, but not of 1,3,4- and 1,3,5-trimethylpiperidines nor 1-methyldecahydroisoquinoline. In other words, only the CH hydrogens adjacent to the ring nitrogen can be catalytically dissociated on the platinum catalyst, leading to epimerization of the α carbon atoms to the nitrogen.

Then, the mechanism of the catalytic isomerization was examined in relation to the hydrogen–deuterium exchange of the CH hydrogens adjacent to the methyl group concerned, as illustrated in Chart 2. *cis*-1,2,3-Trimethylpiperidine was treated with the catalyst in deuterium oxide sufficiently for reaching the isomerization–equilibrium, when hydrogen-2 was completely replaced with deuterium but hydrogen-3 was not at all. This was evidenced by the fact that nuclear magnetic resonance signal of 2-methyl protons was completely deformed from a doublet to a singlet and that of 3-methyl protons still remained a doublet by a thorough

4) For example, N.L. Allinger and J.L. Coke, *J. Am. Chem. Soc.*, **81**, 4080 (1959).
5) The values were obtained following the equation $\Delta G = -RT\ln K$.

treatment with platinum catalyst in deuterium oxide. The same situation was found in catalytic isomerization between *cis* and *trans* 1-methyldecahydroquinolines. Thus, NMR spectral analysis of the products and their methiodides indicated that hydrogen-9 of the isomerized product had been replaced by deutrium. With regard to deuteration of 1,2,6-trimethylpiperidine, when the pure *cis* isomer was treated with platinum in deuterium oxide, the isomerized *trans* isomer at an earlier stage of the reaction contained a little more than one deuterium atom in the molecule, while the *cis* isomer remained included only far less than one deuterium atom. After a thorough treatment, the deuterium contents in the both isomers reached two atoms in each molecule, when the equilibrium had been accomplished in isomerization between the isomers. These facts may lead us to conclusions that isomerization is originated by catalytic hydrogen–abstraction, followed by non-stereospecific hydrogen–addition, and that the hydrogen exchange may almost exclusively occur in the CH group adjacent to the amine nitrogen. In addition to this, it is worth emphasizing that N-methyl nor N-methylene hydrogens were not replaced by deuterium under these reaction conditions. Hydriogen exchange of methyl and methylene hydrogens started at an elevated temperature such as 80°. The details of catalytic hydrogen exchange of amines by platinum will be fully discussed in a forthcoming paper.[6] The fact that quaternary amines such as 1,2,6-trimethylpiperidinium iodide did not undergo isomerization nor deuteration may be of interest in connection with the isomerization mechanism.



(The substrates were used as the hydrochloride forms.)

Chart 2

6) Y. Kawazoe and M. Maeda, *Chem. Pharm. Bull.* (Tokyo), in press.

Experimental

Materials——Alkylpiperidine derivatives were prepared by the authentic preparative methods.[3] Deuterium oxide was purchased from Canada Merck Co. and platinum oxide was obtained from Kawaken Fine-Chemical Co.

Isomerization of *cis*-2,3-Dimethyl Derivative of N-Methylpiperidine——The hydrochloride prepared from 100 mg of *cis* dimethyl derivative[3] was dissolved in 15 ml of H_2O and gently stirred for 48 hr under hydrogen gas atmosphere at room temperature with platinum black prepared from 310 mg of PtO_2. The products were isolated as a mixture of hydrochlorides of the *cis* and *trans* dimethyl derivatives. The NMR spectrum of the mixture of hydrochlorides indicated that it consisted of 65% of the *trans* isomer and 35% of the *cis* one, details of NMR assignment having already been reported in our preceding paper.[3] The hydrochlorides mixture was made into the free bases by addition of conc. aqueous alkali. The gas chromatogram of the free bases extracted from the alkaline slurry with ether told us the same result on the *cis–trans* ratio (condition of gas chromatography: PEG-20M (30%) at 132° at a N_2 gas flow-rate of 21 ml/min). When deuterium oxide and deuterium gas were used instead of ordinary water and hydrogen gas, the NMR spectrum of the mixture of the hydrochlorides produced showed two doublets for 3-methyl protons of the *cis* and *trans* isomers and two singlets for 2-methyl protons of the two isomers, indicating that the only α-CH was replaced by deuterium.

Isomerization of 2,6-Dimethyl Derivative of N-Methylpiperidine——One gram of the hydrochloride of *cis* 2,6-dimethyl-N-methylpiperidine[3] was dissolved in 30 ml of D_2O and stirred at 30° in the presence of Pt catalyst prepared from 3.16 g of PtO_2 in D_2 gas atmosphere. After 24 hr's stirring, a part of the reaction mixture was taken out and evaporated into dryness. The NMR spectrum of the resulting dried material was measured in D_2O, showing that the product included 83% of the *cis* isomer and 17% of the *trans* one. This isomer–ratio was confirmed also by gas chromatography of the free bases liberated from the resulting hydrochloride mixture. The catalytic isomerization of the residual part of the reaction mixture was continued for another 24 hr (the total reaction period, 48 hr). The reaction mixture was worked up in the same way as already described. The NMR and gas chromatographic analyses of the product indicated that the isomer–ratio reached 65% for the *cis* isomer and 35% for the *trans* one. It was confirmed that the isomerization had already reached the equilibrium in this reaction period.

Isomerization of N-Methyldecahydroquinoline——N-Methyldecahydroquinoline was prepared by catalytic hydrogenation of quinoline bisulfate in glacial acetic acid in the presence of Adams' Pt, followed by N-methylation with formaldehyde and formic acid, the product consisting of 60% of the *cis*-fused isomer and 40% of the *trans*-fused one.[7] The isomer–ratio was determined by gas chromatography of the secondary amine derivatives and also by NMR spectroscopy of the methiodides of the N-methyl derivatives. A mixture of the hydrochlorides of 100 mg of *cis* and *trans* 1-methyldecahydroquinolines presently obtained was stirred in 15 ml of D_2O at 30° for 48 hr under D_2 gas atmosphere in the presence of Pt black prepared from 310 mg of PtO_2. After the reaction mixture was made alkaline, the products was thoroughtly extracted with ether. To the ether extract was added a large excess of CH_3I and refluxed for 2 hr. After the evaporation of the solvent, the resulting crystalline solid was dissolved in $CDCl_3$ and the NMR spectrum was measured. Two pairs of two singlets appeared between 3.0 and 4.0 ppm lower than the reference TMS signal. One pair was assigned to two N-methyl protonsignals of the *cis* isomer and the other was to those of the *trans* isomer, the areal-ratio of the two pairs being estimated as 3 to 7, respectively.

Trial of Isomerization of N-Methyldecahydroisoquinoline——N-Methyldecahydroisoquinoline was prepared by catalytic hydrogenation of isoquinoline bisulfate in acetic acid in the presence of Adams' Pt, followed by N-methylation with formaldehyde and formic acid, the product consisting of 90% of the *cis*-fused isomer and 10% of the *trans*-fused one.[8] The hydrochloride mixture of the amines thus obtained were treated as other cases already described. No change was observed at all in the NMR spectrum nor gas chromatogram of the treated material. When deuterated solvent and gas were used, no deuterium was detected in the molecules even by IR spectroscopy. Under more drastic condition such as at an elevated temperature, deuteration proceeded of CH_2 hydrogens next to the nitrogen indeed, but no isomerization did not take place.

NMR Measurements——NMR spectra were obtained with a JMN-60H spectrometer of Japan Electron Optics Latoratory Co. (Tokyo), operating at 60 Mcps.

Acknowledgement The authors are greatly indebted to Dr. Waro Nakahara, Director of National Cancer Center Research Institute, for his encouragement.

7) F.E. King, *J. Chem. Soc.*, **1948**, 1373.
8) B. Witkop, *J. Am. Chem. Soc.*, **70**, 2617 (1948).