Tetrahedron Letters,Vol.26,No.41,pp 5057-5060,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

THE TAUTOMERIC STUDY IN 2-SUBSTITUTED 1,6-DIHYDRO-4,6,6-TRIMETHYL-PYRIMIDINE SYSTEMS

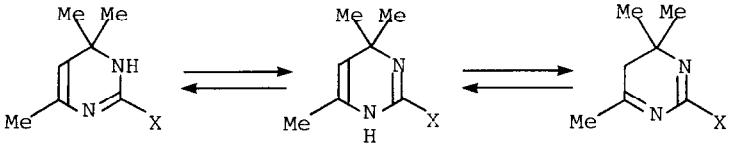
Choji Kashima*, Masao Shimizu, and Yoshimori Omote

Department of Chemistry, University of Tsukuba,
Sakura-mura, Niihari-gun, Ibaraki, 305 Japan

Summary : The novel tautomeric equilibrium between 4,5-dihydro- and 1,6-dihydro isomers was observed in 2-substituted 4,6,6-trimethyldihydropyrimidine systems, besides 1,4-dihydropyrimidine isomers.

The chemistry of dihydropyridines has been widely studied as the model compounds of NAD(P)H[1]. However, the chemistry of dihydropyrimidines, which are regarded as the aza-analogs of dihydropyridines, appears to be scarcely explored. In the case of N-unsubstituted dihydropyrimidines, the location of the double bonds was ambiguous due to their tautomerism. Although 4,4,6-trimethyl-2-phenyldihydropyrimidine (4) and 2-amino-4,4,6-trimethyldihydropyrimidine (8) were denoted as 4,5-dihydropyrimidines (C-type)[2], the structure was later revised from the spectroscopical studies. Silversmith reported that 4 existed as 1,6- (A-type) or 1,4-dihydropyrimidine (B-type)[3]. Also, compound 8 was corrected to be 1,6-dihydropyrimidine (A-type) by Kim et al[4].

Recently, Weis has extensively investigated the tautomerism in dihydropyrimidine systems. In his papers, 1,4-dihydro-6-methyl-2,4-diphenylpyrimidines, which exist in the 1,4-dihydro form in the solid state revealed by X-ray crystallography[5], were isomerized to an equilibrium mixture of 1,6- and 1,4-dihydropyrimidines in the solution[6]. He also reported that 1,2-dihydropyrimidine tautomerized to 2,5-dihydropyrimidine[7].



A 1,6-dihydro **B** 1,4-dihydro **C** 4,5-dihydro

1: X=H **2**: X=Me **3**: X=Pr^{i} **4**: X=Ph
5: X=OEt **6**: X=SMe **7**: X=NMe_2 **8**: X=NH_2

In the course of studies on dihydropyrimidines, we have investigated the substituent effect on the properties of dihydropyrimidine, and here wish to report the tautomerism of 2-substituted 4,4,6-trimethylpyrimidines between 1,6-, 1,4-, and 4,5-dihydropyrimidines.

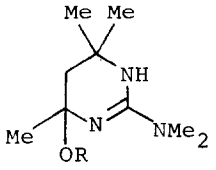
2-Substituted dihydropyrimidines were prepared as follows: 1, 2, 3, 4[2], and 7[4] were prepared by condensation and cyclization reaction between mesityl oxide and amidines or N,N-dimethylguanidine, respectively; 5 and 6[8] were obtained by alkylation of 2(1H)-dihydropyrimidinone and -thione using triethyloxonium tetrafluoroborate and methyl iodide, respectively. Compound 1 was also synthesized by the desulfurization of 2(1H)-dihydropyrimidinethione by Raney nickel.

Weis reported that IR spectroscopy was a good tool for distinguishing of dihydropyrimidine isomers[6]. In his report, in the region of 1600-1700 cm^{-1}, N=C-N-C=C moiety in 1,4-dihydropyrimidines absorbed around 1690 cm^{-1}, while N-C=N-C=C moiety in 1,6-dihydro isomers absorbed around 1650 cm^{-1}. These absorption bands were in good agreement with the N-substituted dihydropyrimidine isomers in which the tautomeric isomers are excluded[9]. For 2-substituted dihydropyrimidines, the absorption band in the 1600-1700 cm^{-1} region was carefully investigated (Table). When IR spectra were measured in chloroform solution, dihydropyrimidines showed two absorption bands in the 1600-1700 cm^{-1} region except in one case (7), that is, in almost cases, N-unsubstituted dihydropyrimidines existed as the mixture of 1,6- (A) and 1,4-dihydro isomers (B) in solution. For 2-dimethylamino derivatives (7), because only one peak at 1650 cm^{-1} observed in IR spectra in the region of 1600-1700 cm^{-1}, it was suggested that the 1,4-dihydropyrimidine isomer did not exist. Furthermore, in

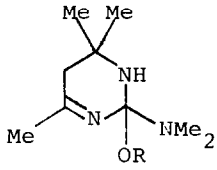
Table

	IR(cm^{-1}) (1600-1700)		^{1}H-NMR(δ)[a]	^{13}C-NMR(δ)[a]	UV(nm)[b]	Ratio of C[a]
	in KBr	in $CHCl_3$	(5-H)	(5-C)	(λ_{max})	(%)
1	1630, 1690	1630, 1690	4.35	106.5	266	0
2	1650	1670, 1690	4.40	106.1	265	5
3	1650	1640, 1690	4.43	106.6	275	0
4	1650, 1690	1650, 1680	4.56	106.8	306	10
5	1660, 1700	1650, 1690	4.46	106.3	244	20
6	1645	1640, 1690	4.49	107.6	269	31
7	1650	1650	4.41	103.6	267	46

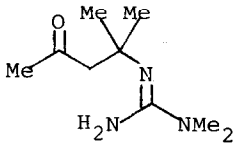
a) Measured in $CDCl_3$. b) Measured in EtOH.



9



10



11

(R=H or Me)

the ^{13}C-NMR spectra, chemical shift of C-5 carbon of compounds 1-6, whose values should be shown as an average of two kinds of compounds (A and B), were different from that of 7.

When the ^{1}H-NMR spectrum of compound 7 was measured in $CDCl_3$, unexpected peaks at δ 1.07, 1.79, 1.96 and 2.94 ppm whose ratio was 6:3:2:6 were observed besides the signals of 1,6-dihydro isomers[10]. Also, in the ^{13}C-NMR spectrum, an unexpected triplet peak was observed at δ 41.0 ppm. From these NMR spectral data, the structure of the unexpected compound could be assumed as 4,5-dihydropyrimidine (C-type), a water adduct of the dihydropyrimidine ring on the 6- or 2-carbons (9 or 10), a ring-opened product (11), or dimers reported by Wendelin and Harler[11]. When 7 was dissolved into solvent, the new peaks gradually increased and reached to equilibrium with time. The proportion of the new peaks was higher in aprotic solvent, chloroform, than in protic solvent, methanol. Furthermore, in mass spectrum of the crystal, molecular ion peak was observed at m/e 167. From these observation, the new peaks were attributed to 4,5-dihydro-4,4,6-trimethyl-2-dimethylaminopyrimidine (C-type), which is an isomer of 1,6-dihydropyrimidine. The similar isomerization was observed in the other dihydropyrimidines, and the ratios evaluated from ^{1}H-NMR spectra are shown in Table. When the ratio of isomers was compared with 3 and 7 whose bulkiness of the substituents on 2-position was estimated to be similar, an apparent difference was observed in the ratio of the C-type dihydropyrimidine. This fact suggested that the isomerization should be attributed to electronic effect. This isomerization was notably observed in the dihydropyrimidines whose substituents on C-2 carbon were heteroatoms or a phenyl group.

It was concluded that the novel equilibrium between 4,5-dihydro- and 1,6-dihydropyrimidines was observed in 2-heteroatom substituted 4,6,6-trimethyl-dihydropyrimidine systems. The substituents of dihydropyrimidines have influence on their degree of isomerization.

REFERENCES AND NOTES

1) U. Eisner and J. Kuthan, Chem. Rev., 72, 1 (1972); D. M. Stout and A. I. Meyers, Chem. Rev., 82, 223 (1982).
2) W. Traube and R. Schwartz, Ber, 32, 3163 (1899).
3) E. F. Silversmith, J. Org. Chem., 27, 4090 (1962).
4) Y. H. Kim, C. M. Yoon, and N. J. Lee, Heterocycles, 16, 49 (1981).
5) A. Weis and F. Frolow, J. Chem. Soc., Chem. Commun., 1982, 89.
6) A. L. Weis, Tetrahedron Lett., 23, 449 (1982).
7) A. L. Weis and R. Vishkautsan, Chem. Lett., 1984, 1773; Heterocycles, 23, 1077 (1985).
8) B. H. Chase and J. Walker, J. Chem. Soc., 1955, 4443.
9) C. Kashima, M. Shimizu, A. Katoh, and Y. Omote, Tetrahedron Lett., 24, 209 (1983); J. Chem. Soc., Perkin Trans. 1, 1983, 1799.
10) For 7A: ^{1}H-NMR (δ, $CDCl_3$) 1.20 (s, 6H), 2.16 (d, 3H, J=1 Hz), 3.00 (s, 6H), 4.0 (br s, 1H), and 4.41 ppm (q, 1H, J=1 Hz).
11) W. Wendelin and A. Harler, Monatsh Chem. 105, 563 (1974).

(Received in Japan 13 July 1985)