THE STRUCTURAL STUDY ON 2-AMINODIHYDROPYRIMIDINE DERIVATIVES

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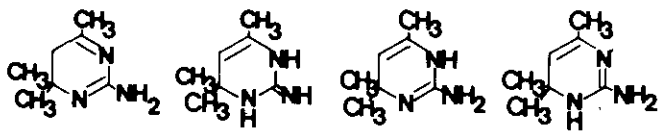
Abstract - The structures of dihydropyrimidines synthesized from mono- or dialkylguanidine with methyl acrylate were assigned as 1-alkyl-2-amino-**(6b)** or 1-alkyl-2-alkylamino-5,6-dihydropyrimidin-4-one**(6d)** by comparing ^{1}H nmr, ir, and uv spectral data with those from **6b** and **6d** synthesized by the other route. The λ_{max} values of the dihydropyrimidines showed significant differences from those of the hydrochlorides whose significant blue shifts are thought to be a good evidence and a tool for the conjugative system of the two double bonds in 2-aminodihydropyrimidines.

The chemistry of dihydropyrimidines which has been virtually unknown due to the instability of these compounds and the difficulty for purification, has been recently well studied and discussed[1]. But the available literature data on 2-aminodihydropyrimidines are quite speculated. 2-Amino-4,4,6-trimethyl-3,4-dihydropyrimidine has been demonstrated to show a selectivity for the sodium channel in the muscle membrane[2] qualitatively similar to that possessed by tetrodotoxin[3] and saxitoxin[4] which are highly potent non-protein nurotoxin. Dihydropyrimidines have been also known to be important intermediate in the catabolism and anabolism of pyrimidines.[5-7] However the structure of dihydropyrimidines is still uncertain due to their instability and impurity. Earler, Traube and Schwarz[8] reported that dihydropyrimidines obtained by the cyclization of guanidine with mesityl oxide is the structure **1**.

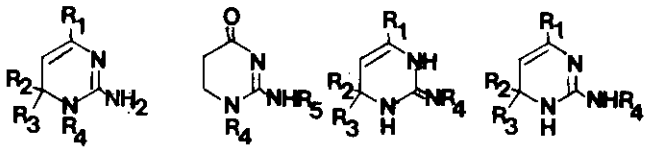


1 **2** **3** **4**

Later, Wendelin and Harler[9,10] have revealed that the reaction of guanidine and mesityl oxide afforded a mixture of dihydropyrimidines, **2**, **3** or **4**, and its dimer. Recently, they[10] reported

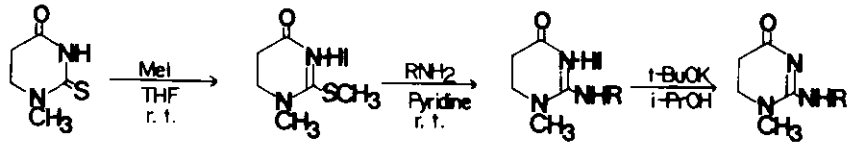
the possible structure of the dihydropyrimidine synthesized by the reaction of N-alkylguanidine with mesityl oxide may be **7**.

Previously, we reported facile synthesis of 2-aminodihydropyrimidine derivatives by the reactions of substituted guanidines with α, β-unsaturated ketones[11] and methyl acrylate[12] respectively. There have been very few spectral data on 2-aminodihydropyrimidines. In this paper, we propose plausible structures of **5** and **6** by comparing spectral data of various good model compounds of 2-aminodihydropyrimidines.



5 **6** **7** **8**

1-Methyl-2-methylamino-5,6-dihydropyrimidin-4-one was synthesized unequivocally through other synthetic route(Scheme 1). 1-Methyl-2-thio-5,6-dihydrouracil(**9**)[13] was S-methylated by methyl iodide to afford white precipitate (**10**) which was easily converted to 2-amino-1-methyl-5,6-dihydropyrimidin-4-one hydroiodide(**11a**) or 1-methyl-2-methylamino-5,6-dihydropyrimidin-4-one hydroiodide(**11b**) by the reaction of **10** with aqueous ammonia or methylamine respectively. The compounds **11a** and **11b** were easily freed by t-butoxide in isopropanol. The freed product of **11a** or **11b** was compared with the dihydropyrimidinone synthesized from N-methylguanidine or N,N'-dimethylguanidine with methyl acrylate. Their spectral data of ^1H nmr, ir, uv, and mp were identical: namely position of methyl groups was proved to be correct by ruling out a possibility of 3-methyl isomer.



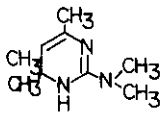
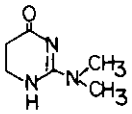
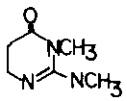
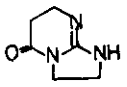
9 **10** R=H, **11a** CH3, **11b** **6**

Scheme I

In order to discuss the position of double bond in dihydropyrimidines, we measured the λ_{max} values of 2-aminodihydropyrimidines and 2-aminodihydropyrimidine hydrochlorides[14](Table 1). The $-C_5=C_6-$ bond of **8a-8c** could be readily confirmed[11] by the vinyl proton(δ4.26 in DMSO-d_6) at C-5 position. Since λ_{max} and ε value of **8d** which must have only endo double bond are close to those of **8a-8c**, the two double bonds of **8a-8d** are also thought to have conjugative systems($-C_2=N-C_6=C_5-$). The λ_{max} values of various dihydropyrimidines are much different from those of

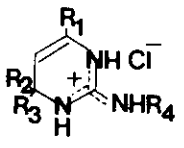
hydrochlorides especially the N-alkylated dihydropyrimidines synthesized from N-substituted guanidines(**8b**, **8c**, and **6b-6d**) show more significant blue shifts between free forms and hydrochlorides.

Table 1. UV spectra of 2-aminodihydropyrimidines

Run	Dihydropyrimidine		Solvent	λ_{max},nm(ε)	λ_{max},nm(ε) of salt[14]
1	R_1=R_2=R_3=Me, R_4=H	(**8a**)	i-PrOH	250(2.29×10^3)	240(2.75×10^3)
2	R_1=R_2=R_3=Me, R_4=Me	(**8b**)	i-PrOH	266(3.12×10^3)	236(3.80×10^3)
3	R_1=R_2=R_3=Me, R_4=Et	(**8c**)	i-PrOH	260(3.66×10^3)	240(3.90×10^3)
4		(**8d**)	i-PrOH	269(3.41×10^3)	-[a]
5	R_4=R_5=H	(**6a**)	H_2O	240(5.24×10^3) 223(1.90×10^4)	257(1.07×10^3) 220(3.51×10^3)
6	R_4=Me, R_5=H	(**6b**)	MeOH	240(1.39×10^4) 205(1.41×10^4)	222(5.64×10^3)
7		(**6c**)	MeOH	236(1.44×10^4)	219(7.65×10^3)
8	R_4=R_5=Me	(**6d**)	MeOH	238(1.06×10^4) 220(1.12×10^4)	219(7.65×10^3)
9[15]		(**12**)	EtOH	213[b]	208[c]
10[15]		(**13**)	H_2O	214[d]	212[e]

a. The compound is not stable enough to measure the λ_{max} and ε value of HCl salt.
b. 0.01N NaOH in EtOH
c. 0.01N HCl in EtOH
d. pH 3 buffer
e. 0.01N NaOH in H_2O

In the case of **12**(Run 9) and **13**(Run 10) which cannot have conjugative system, the λ_{max} values of **12** and **13** are very close not only to those of the hydrochlorides but also to those of the hydrochlorides of **6b-6d**. This is a good evidence for no clean conjugative system of $-C_2$=N-$-C_6$=C_5- in the hydrochlorides. The protonation to the guanidine moiety has been known to be delocalized, because the salt of guanidine possesses very stable conjugative system as shown below. When the guanidine moiety is protonated, the conjugation between two double bonds in dihydropyrimidines is much weakened by the more stable resonance of guanidine moiety and the λ_{max} value of conjugative system in dihydropyrimidine should be blue-shifted.



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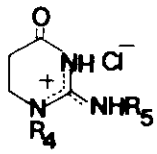

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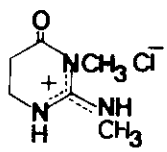

12

In case of no conjugative systems in **12** and **13**, λ_{max} values of dihydropyrimidines are actually almost the same to those from the hydrochlorides (Run **9** and **10**), because the protonations of guanidine moieties almost give no electronic effects on the carbonyl groups in **12** and **13**. The λ_{max} (269nm) and $\varepsilon(3.41\times10^3)$ values of **8d** are close to those of **8a**, **8b**, and **8c**. The double bond of the imine in **7** can not be formed because of N,N-disubstituted amine by two methyl groups. Since the two double bonds of **7** are not in conjugative system, uv spectrum of **7** should be different from **8a-8d**. Thus, the structure **7** can be ruled out. Now we concluded that the dihydropyrimidines have conjugative endo double bond in protic solvent(not **7**, but **6** and **8**), and they show significant blue shift(about 20-30nm) in λ_{max} in case of converting to hydrochlorides. Furthermore, the ir absorption bands provided an excellent tool[16] for the differentiation of the two isomers in the N-substituted dihydropyrimidines, and the lower frequencies ($1670cm^{-1}$>) in the conjugative system(**8a-8c** and **6a-6d**)[17] show another evidence for $-C_2=N-C_6=C_5-$ system instead of **7**. Thus it is best explained that 2-aminodihydropyrimidines have the conjugative endo double bond(**6** and **8**) in protic solvents by the significant blue shifts in case of the hydrochlorides.

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