THE CRYSTAL AND MOLECULAR STRUCTURE OF 4,6,6-TRIMETHYL-2-PHENYL-1,6-DIHYDROPYRIMIDINE[1]

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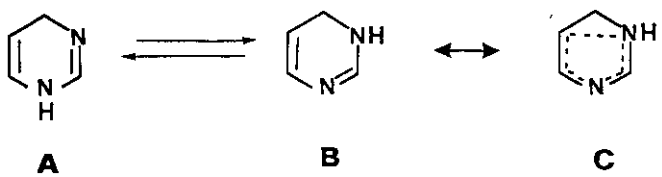
Abstract — An X-ray crystallographic study of dihydropyrimidine (III) has shown that in the solid state it exists in the 1,6-dihydro form (IIIb). Both tautomers IIIa and IIIb were detected by an NMR study of III in a DMSO-d_6 solutions.

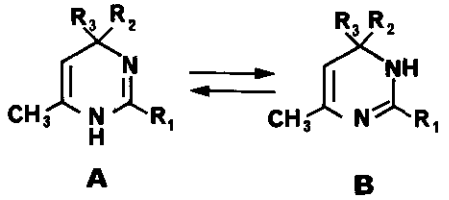
Dihydropyrimidines easily convertible to pyrimidines possess important antioxidant, membranotropic and pharmacologic properties[2]. The chemistry of dihydropyrimidines is virtually unknown because of the widely accepted opinion regarding the instability of these compounds and the absence of convenient isolation and purification methods. In addition to this, there is a lack of data on the stabilization - destabilization effects of substituents on these ring systems. Moreover, the question concerning the structure and relative stabilization of the tautomeric 1,4- and 1,6-dihydropyrimidines is open. The available literature data on the structure of 1,6- and 1,4-dihydropyrimidines has been quite speculative. Alternative preferences for either structure have been proposed with insufficient information to justify the suggested assignments. The majority of articles dealing with 1,4- and 1,6-dihydropyrimidines describe the tautomeric compounds in one of the possible forms, usually form B, without any discussion of the tautomerism[3]. Other publications suggest either complete delocalization C [4] or a time average of rapidly interchanging tautomers A and B[5], but individual structures could not be pinpointed.



A **B** **C**

Scheme I

We have undertaken a systematic study of dihydropyrimidines and recently reported a preliminary account of the observation of each individual tautomer I_A and I_B of 6-methyl-2,4-diphenyldihydropyrimidine (I) in DMSO and HMP solutions[6].



I $R_1=R_2=Ph$ $R_3=H$
II $R_1=Ph$ $R_2=2\text{-furyl}$ $R_3=H$
III $R_1=Ph$ $R_2=R_3=Me$
IV $R_1=R_2=R_3=Me$
V $R_1=NH_2$ $R_2=R_3=Me$

Scheme II

Furthermore it was shown[7] that in the solid state compound I exists in the 1,4-dihydro form (I_A) and by comparison of the spectral (IR, UV, NMR) data it became possible to make definitive structural assignments of both tautomers. However all attempts to isolate I_B in crystalline form failed.

The studies now reported were aimed at further demonstrating the validity of our spectral *(IR, NMR) interpretations in the assignments of tautomers A and B.*

Earlier Traube and Schwarz reported[8] the dihydropyrimidine III as the 4,5-dihydro structure. Later Silversmith[5a] revealed that NMR and IR spectral data contradicted the 4,5-dihydro structure but was consistent with the tautomeric structures III_A and III_B, however he was unable to decide between them. Thus, no definitive structure had been proposed earlier for this compound.

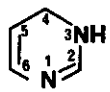
Recently we reported that characteristic absorptions in the 1600-1700 cm^{-1} region of the IR spectra provided an excellent tool for differentiation of the tautomers[1].

On the basis of the IR band at 1652 cm^{-1} in KBr, we proposed that 4,6,6-trimethyl-2-phenyl-dihydropyrimidine[5a] in the solid state has the structure of the 1,6-tautomer (III_B), by comparison of its IR spectrum to that of I_A and I_B (see Table).

A single crystal X-ray diffraction analysis was therefore made to clarify this situation, the result of which has confirmed this suggestion, as shown in Figure I.

Crystal data: The single crystals of dihydropyrimidine (III) obtained from petroleum ether (30 - 40°C) are colorless cubes, m.p. 98-98.5°. They are monoclinic, space group $P2_1/C$, a=16.286(1), b=17.095(1), c=18.826(1)Å, β=109.31°, z=16. Intensities data of 6316 unique reflections were measured on a Nonius CAD-4 diffractometer with Mo-Kα radiation. The structure was solved by direct methods using MULTAN-80, and refined by bloc-diagonal least square to quite high R=0.1, owing to disorder in two out of four independent molecules. Low temperature study of this phenomena is now under research.

Ttable. Selected NMR and IR data for structural and spectral correlations of tautomeric 1,4- and 1,6-dihydropyrmidines.

Compounds	 A		 B		Average spectra NMR	Ratio
	NMR DMSO-d_6, δ, p.p.m.	IR, cm^{-1}	NMR DMSO-d_6, δ, p.p.m.	IR, cm^{-1}	δ, p.p.m.	A : B
I	H^4-5.26 H^5-4.39 NH-8.56	1698-1700 KBr and solutions	H^4-5.21 H^5-4.87 NH-8.05	1646-50 solutions	DMSO-d_6: 8.36(NH), 5.24(H^4), 4.59(H^5), 1.79(CH_3) $CDCl_3$: 5.34(H^4), 4.70(H^5, q, J=1.1 Hz), 1.90(CH_3, d, J=1.1Hz)	3:2 DMSO-d_6 3:4 $CDCl_3$
II	H^4-5.29 H^5-4.36 NH-8.61	1698-1700 KBr and solutions	H^4-5.26 H^5-4.84 NH-8.02	1646-50 solutions	$CDCl_3$: 5.41(H^4), 4.68(H^5, q, J=1.0) 1.82(CH_3, d, J=1.0)	9:1 DMSO-d_6
III	H^5-4.23 NH-8.38	1690-94 solutions	H^5-4.63 NH-in arom. (7.30-7.85)	1650-54 KBr solutions	DMSO-d_6: 4.45(H^5, q, J=1.1); 1.75(CH_3, d, J=1.1) 1.18($2CH_3$) $CDCl_3$: 4.57(H^5, q, J=1.1), 1.77(CH_3, d, J=1.1)	9:11 DMSO-d_6
IV	H^5-4.16 NH-8.32	1690-94 solutions	H^5-4.56 NH-7.80	1650-54 KBr and solutions	$CDCl_3$: 4.41(H^5, q, J=1.1) 1.93($CH_3^{(2)}$) 1.75 ($CH_3^{(6)}$, d, J=1.1); 1.17($2CH_3^{(4)}$)	-
V	-	1700 (?) KBr	-	-	DMSO-d_6: 5.08(3H, NH), 4.23(H^5, q, J=1.1) 1.54(CH_3, d, J=1.1) 1.05 ($2CH_3$)	-

* The correct nomenclature of structure B is 1,6-dihydropyrimidine; we have numbered in as shown only for the sake of convenient comparison of tautomers A and B.

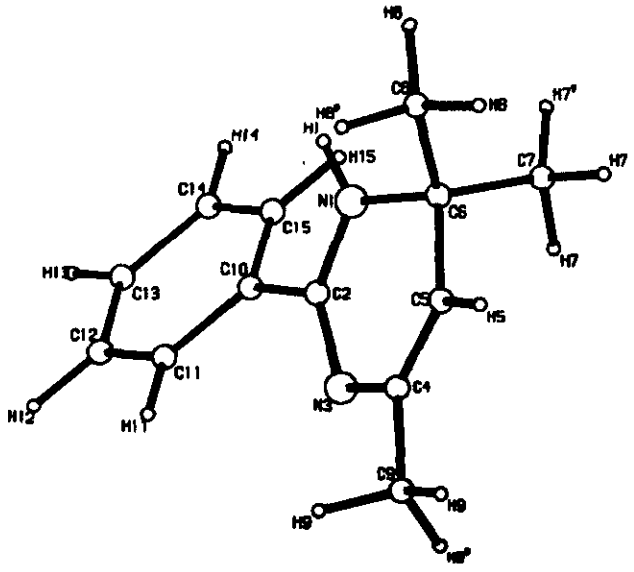


Figure I. The computer-plotted molecular structure of 4,6,6-trimethyl-2-phenyl-1,6-dihydropyrimidine III_B. Selected important bond lengths: N(1)-C(2), 1.35; C(2)-N(3), 1.29; C(3)-C(4), 1.42; C(4)-C(5), 1.32; C(5)-C(6), 1.49; C(6)-N(1), 1.47 Å.

Moreover, taking into account the recently published[1] factors affecting the possibility of observation of similar tautomerism in dihydropyrimidine systems, both tautomers may be observed clearly in the NMR spectrum when measured in DMSO-d_6 solutions.

It should be noted that, solutions of III, IV are sensitive to oxygen and undergo slow decomposition. However in the crystalline state at low temperature these compounds are quite stable for long periods of time, but undergo rapid decomposition to red colored substances when exposed to air and light at room temperature[9].

We prepared V by all known methods[8,10] and in all cases isolated identical white crystals, m.p. 164°. On the basis of the IR data of 2-aminodihydropyrimidine (V) we suggest that it has 1,4-dihydrostructure by comparison with other members of the Table. Its X-ray diffraction results and tautomeric properties will be published shortly.

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