

DIHYDROPYRIMIDINES: SYNTHESIS, STRUCTURE AND TAUTOMERISM*

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Abstract - This review describes the preparation of the dihydropyrimidines, the structure, stability and tautomerism of these systems and the rearrangements in which these compounds can be involved.

This review involves the following contents

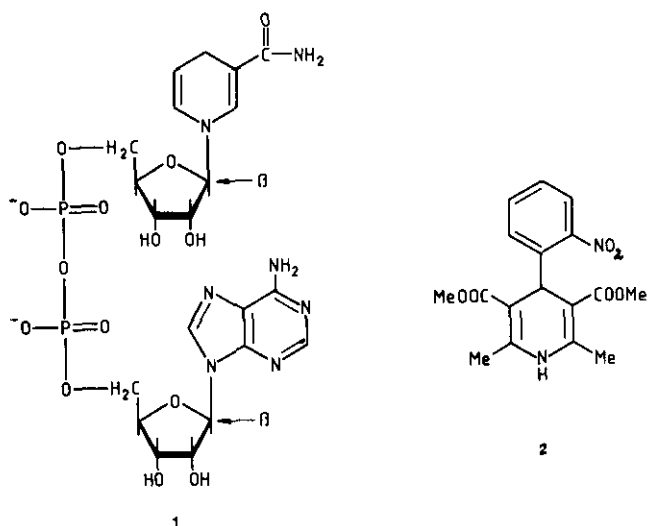
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* Dedicated to Professor V.P. Mamaev on the occasion of his 60th birthday

I. INTRODUCTION

The preparation, chemical and physical properties of aromatic six-membered nitrogen-containing heterocyclic compounds (e.g. pyridines, diazines, etc.) and their occurrence and function in biological systems have been extensively studied. However, the chemistry of reduced azines has been largely unexplored, with the exception of the dihydroazines (DHA) that are lately attracting particular attention. These compounds, which are actually diverse nitrogen analogs of cyclohexadienes and previously thought to be highly unstable, have in recent years achieved some prominence, due to recent advances in theoretical, bio- and medicinal chemistry.

Particularly dihydroazines containing the 1,4-dihydropyridine moiety¹ are of great interest to biochemists, as this structure plays an important role at the active site of the "hydrogen - transferring coenzyme" NADH (I) (reduced nicotinamide adenine dinucleotide). In order to better understand the NADH biochemistry, it has become important to synthesize a wide range of DHA derivatives - both chiral and achiral - for use as NADH analogs.² Dihydropyrimidinic analogs of the dihydronicotinamide moiety of NADH provide new opportunities to modify metabolic processes and clarify the mechanisms of biological redox reactions involving NADH. Moreover, since C-bound nucleosides have been found to exhibit novel antiviral and antitumor activity³, it would also be of interest to prepare analogous C-substituted dihydropyrimidinic nucleosides.

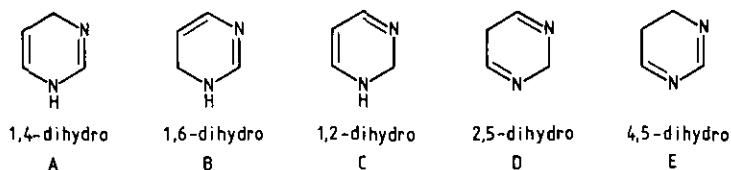


In the area of drug development, the chemistry of DHA shows great promise, particularly since the 4-aryldihydropyridines exhibit powerful vasodilating activities via blocking of the calcium channel and modifying the movement of Ca^{++} into and within cells. The explosive activity in this

area of heterocyclic synthesis has produced an exponential growth in patent applications and papers, and has led to the marketing of a new, effective drug for treating cardiac patients, nifedipine (2).⁴ Other active 4-aryldihydropyridine derivatives, such as nimodipine and nicardipine (cerebral vasodilators) and nitrendipine (an antihypertensive) are presently undergoing clinical trials.⁵ Further interest in DHA chemistry was stimulated by the demonstration of drug-delivery systems using dihydropyridines to achieve enhanced transport of medication across biological membranes.⁶

Most of the information available today centers around the dihydropyridines, although a few reports dealing with dihydropyrazines⁷ and dihydropyridazines⁸ have appeared. Until recently, papers describing the synthesis and chemistry of dihydropyrimidines were very limited. Only a handful dealt with successful synthesis, and a few with chemical properties - for example, reaction of dihydropyrimidines with electrophiles, and comments relating to "instability" and "susceptibility to oxidation". Since we could not discern why introduction of a nitrogen atom at the β -position of dihydropyridine should lead to decreased stability, we entertained the thought that perhaps not so much the instability of the dihydropyrimidines, but rather the synthetic approaches used to obtain them, caused the inaccessibility of the compounds. So, we initiated a detailed study of the preparation and properties of dihydropyrimidines. As we were able to develop a simple route for synthesis of a model dihydropyrimidine, which exhibit amidinic tautomerism, the door was opened to expand our knowledge of dihydropyrimidine chemistry. This account relates to the work we have achieved in this area; we incorporate in this account only monocyclic dihydropyrimidines being unequivocally identified. Particular attention will be given to those dihydropyrimidines bearing no substituents on the ring nitrogen(s), and which can undergo oxidation to the corresponding pyrimidines.

All the dihydropyrimidines being described in this Review can be present in several tautomeric structures. In order to differentiate them we used the capitals A, B, C, D, E. The capitals A, B, C, refer to the cyclic enamines, in which the lone part of the p-electrons of the sp^3 nitrogen can conjugate with the four π -electrons of the diene, and the capitals D, E to the cyclic imines, in which such conjugation cannot occur.



II. SYNTHESIS

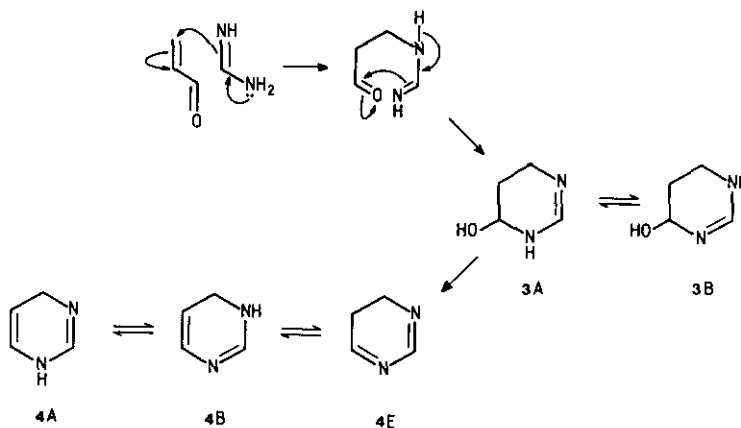
The methods for preparing dihydropyrimidines can be conveniently divided into two main groups: cyclizations of acyclic fragments and modifications of pre-existing pyrimidine rings.

II.a Cyclization Methods

II.a.1 From α,β -Unsaturated Carbonyl Compounds.

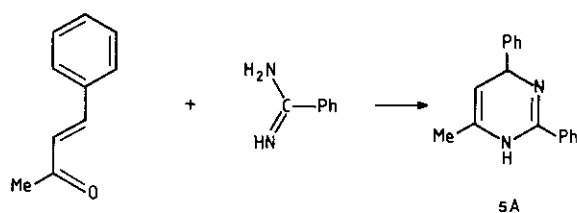
The reaction of amidines with readily available α,β -unsaturated carbonyl compounds seems an attractive <3+3> approach to obtain dihydropyrimidines. However, until recently, only a few reactions of this type were known as the result of a fortuitous combination of reaction conditions and starting materials.¹⁰

Consideration of the possible mechanisms of dihydropyrimidine formation from α,β -unsaturated carbonyl compounds and amidines suggested that the reaction occurs via nucleophilic attack by amidine at the activated double bond (Michael-type addition), followed by ring closure and dehydration (see Scheme 1).



Scheme 1

A new approach to obtain 6-methyl-2,4-diphenyldihydropyrimidine (5a), originally synthesized by Ruhemann¹⁰ and subsequently by Heyes and Roberts¹¹, involves the condensation of benzalacetone and benzamidine in benzene along with azeotropic removal of the water.¹² The method however failed when attempting to synthesize other dihydropyrimidines, particularly those with fewer and less bulky substituents.

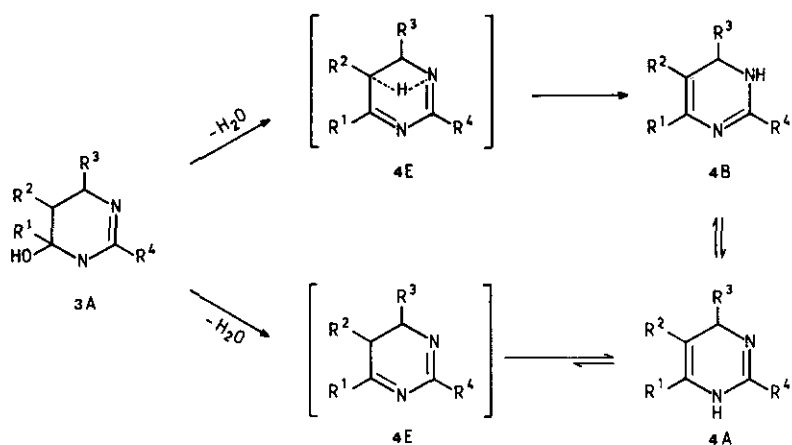


A new attempt to prepare these compounds, namely first preparation and isolation of the hydroxytetrahydropyrimidine (3), followed by dehydration of (3) to the dihydropyrimidine (4), proved to be successful. Applying this strategy, a nearly quantitative yield of 6-hydroxy-1,4,5,6-tetrahydropyrimidines (3) could be easily achieved under mild conditions, and optimal methods for carrying out the dehydration reaction were developed. This new and versatile synthetic route indeed enables the preparation of a large variety of dihydropyrimidines.¹³

These results induced us to attempt the synthesis of the parent 1,4(1,6)-dihydropyrimidine, a goal long sought by synthetic chemists. Past attempts to prepare it from acrolein failed.^{10,14,15} However, using the two-step method, 6-hydroxytetrahydropyrimidine (3) was prepared in high yield from acrolein and formamidine. Dehydration of this product was carried out by boiling in dimethoxyethane (or in other solvents, such as acetonitrile or DMF), yielding the unsubstituted dihydropyrimidine (4). Unfortunately, under the conditions used, 4 was extremely unstable and could not be isolated in a pure state. However, NMR and MS spectra verified its presence.¹⁶ By applying this method to the reaction of acrolein with acetamidine or benzamidine, a high yield of both 2-methyl- or 2-phenyl-dihydropyrimidine was achieved.^{16,17} The 2-phenyl derivative is stable, whereas the 2-methyl product decomposes, though not as rapidly as the parent molecule. In all these reactions involving acrolein, polymerization of the starting material was prevented by addition of hydroquinone.

Dihydropyrimidines functionalized at position 5, which display interesting activities as calcium antagonists, membranotropic agents and antioxidants, were also prepared in good yields. The dehydration was particularly successful when using acid catalysis or acetic acid as the solvent.¹⁸ These results are reminiscent of the classical synthesis of Schiff bases, in which the dehydration of the N,O-hemiacetal intermediates is accelerated by general acid catalysis.¹⁹

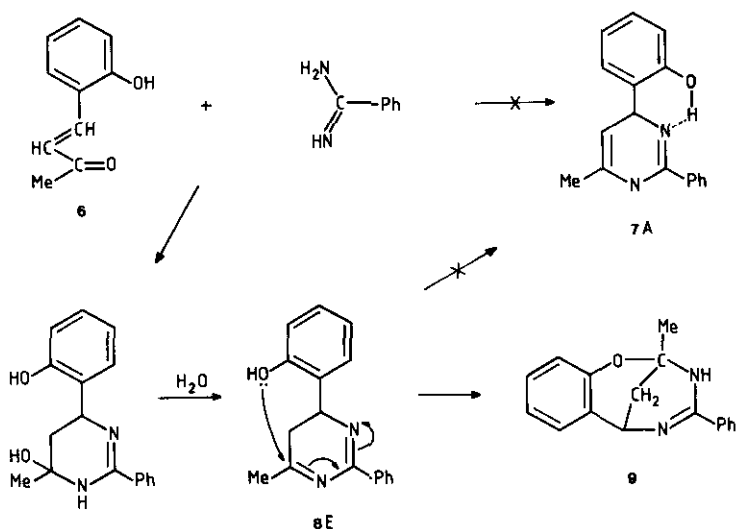
The initial product of dehydration of hydroxytetrahydropyrimidine (3) is probably the unstable 4,5-dihydropyrimidine **4B**, which presumably undergoes either thermal suprafacial [1,5]-hydrogen migration to the corresponding 1,6-dihydropyrimidine (**4B**) or imine-enamine tautomeric rearrangement to the 1,4-dihydropyrimidine **4A**. (Scheme 2).



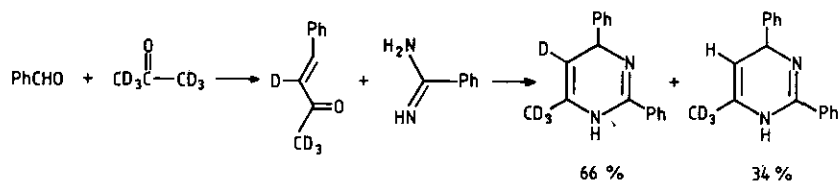
Scheme 2

Apparently, the rate of hydrogen migration is fast, since 4,5-dihydropyrimidines were neither isolated nor detected spectroscopically. However, some indirect, but not unequivocal, proofs for the intermediacy of 4,5-dihydropyrimidines were obtained: in the reaction of *o*-hydroxybenzalacetone (6) with benzamidine, instead of the desired dihydropyrimidine (7A) (which is stabilized by intramolecular hydrogen bonding), the corresponding bridgehead compound (9) was isolated.²⁰ (See Scheme 3).

The key step in this reaction is likely the formation of highly reactive 4,5-dihydropyrimidine (8E), in which the phenolic hydroxy group rapidly attacks position 6 before proton migration occurs to the dihydropyrimidine 7A.



Moreover, for specific assignment of the protons at C(4) and C(5), in the course of structural investigations via NMR, the deuterated dihydropyrimidine was prepared.²¹

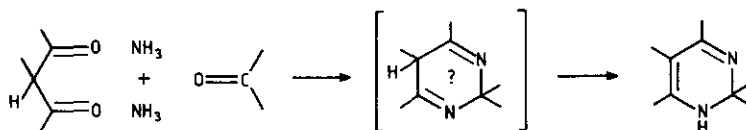


The ratio of deuteration at position 5 is what would be expected from a kinetic isotope effect during the isomerization of 4,5-dihydropyrimidine to the more stable tautomeric 1,4- and 1,6-dihydro compounds.

The mechanism of this hydrogen migration needs further study. It would be interesting to compare the rates of and substituent influences on this migration with the similar processes in the last step of Hantzsch's synthesis of dihydropyridines, and in hydrogen migration in dihydropyridazine series.

II.a.2 From β -Dicarbonyl Compounds.

The four-component condensation reaction of β -dicarbonyl compounds with ammonia (or ammonium salts) and carbonyl-containing substances seems to be a convenient and rather promising <3+1+1+1>-fragment approach for the preparation of 1,2-dihydropyrimidines (Scheme 4).



Scheme 4

This reaction is nearly identical to the classical Hantzsch synthesis of dihydropyridines, with only the molar ratio of starting materials being changed. However, only isolated examples of its application are found in the literature. Kröhnke and coworkers²² were the first to attempt this method, but its use for the successful isolation of 1,2-dihydropyrimidines, was only achieved by Hoffmann and coworkers.²³ Other authors subsequently employed this approach for various purposes.²⁴

A recent report of the quantitative preparation of amino vinyl ketones²⁵ from ammonium acetate and

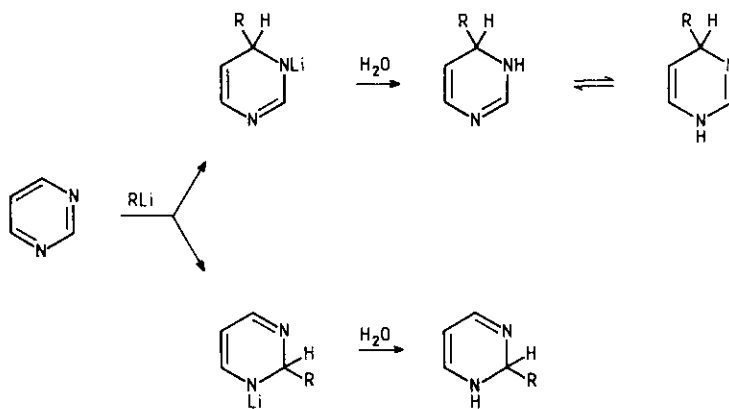
β -dicarbonyl compounds stimulated the development of a modified <4+1+1> approach for preparation of 1,2-dihydropyrimidines in high yields.²⁶ A similar preparation utilizing a gem-diamine containing two trifluoromethyl groups was also reported.²⁷ It is surprising that methylenediamine²⁸ has not been used as a starting material for this reaction.

In addition, *N*-substituted 1,2-dihydropyrimidines have been obtained in an aluminium chloride-catalyzed reaction of diimines, carbonyl compounds or their acetals²⁹ and via imidoalketenimine rearrangement at room temperature.³⁰ Polish workers claimed the formation of dihydropyrimidines by reaction of methyl aluminates with acrylonitriles.³¹

II.b Pyrimidine Derivatives as Starting Materials

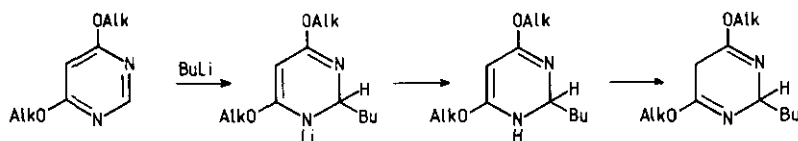
II.b.1 Addition of Organometallic Reagents

Several reactions of organolithium compounds or Grignard reagents with pyrimidines or its derivatives have been reported to give, after suitable workup, a mixture of 2- and 4-substituted pyrimidines.^{9,32} Although these reactions occur via unstable dihydropyrimidines, most of these early investigations were aimed at preparing substituted pyrimidines, and therefore, the dihydropyrimidine intermediates were never isolated and very seldom identified. The action of Li-organic reagents (particularly, aryl and hetaryl lithium) on pyrimidine and derivatives has been used recently for the preparation of dihydropyrimidines.^{33,34,35}



This addition usually occurs at the unsubstituted positions. Thus, in the case of pyrimidines, a mixture of 1,6- (or 1,4-) and 1,2-dihydropyrimidines is obtained as a result of nucleophilic addition to the C=N bonds; the formation of 1,6- (or 1,4-) dihydropyrimidines predominates. When only a single unsubstituted or sterically less-hindered position is available, one product results.³⁶

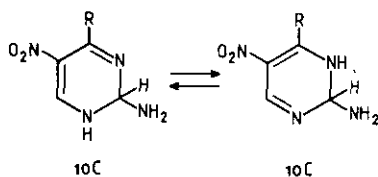
An interesting example of an unusual 2,5-addition of organometallics is the addition of butyllithium to 4,6-dialkoxyypyrimidines to give the 2-butyl-4,6-dialkoxy-2,5-dihydropyrimidines. The formation of these compounds probably occurs via the intermediate 1,2-dihydropyrimidines³⁷, which most likely undergo a tautomeric hydrogen shift. A series of 2,5-dihydropyrimidines of this type was prepared analogously.³⁸



II.b.2 Addition of Neutral Nucleophiles

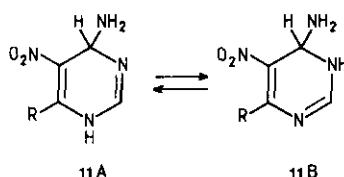
Recently it has been established^{38a} that 5-nitropyrimidine when dissolved in liquid ammonia at -45°C undergoes covalent addition at C-2, yielding 2-amino-5-nitro-1,2-dihydropyrimidine **10** ($\text{R} = \text{H}$). Adduct **10** ($\text{R} = \text{H}$) is unstable in the liquid ammonia at -45°C and slowly converts at -35°C to the 4-amino adduct **11** ($\text{R} = \text{H}$). This 4-amino adduct formation occurs very fast when liquid ammonia is allowed to react at room temperature. 2-R-5-nitropyrimidines ($\text{R} = \text{CH}_3, \text{SCH}_3, \text{C}_6\text{H}_5, \text{SO}_2\text{CH}_3$) give with liquid ammonia at -35°C exclusive addition at C-4; 4-methoxy-5-nitropyrimidine only yields the C-2 adduct. All attempts to isolate these adducts failed. Since they are very stable in liquid ammonia; their ^1H -, ^{13}C - and ^{15}N -NMR spectra could easily be measured and their tautomeric structures identified.

[1,5]-hydrogen shift



$\text{R} = \text{H}, \text{OCH}_3$

Amidine tautomerism



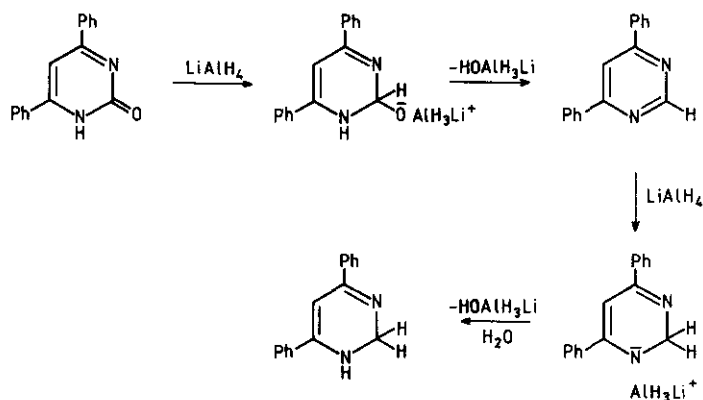
$\text{R} = \text{H}, \text{CH}_3, \text{SCH}_3, \text{SO}_2\text{CH}_3, \text{C}_6\text{H}_5$

II.b.3 Reduction with Complex Metal Hydrides

The reduction of pyrimidines by complex metal hydrides to yield dihydropyrimidine has not been systematically investigated. Earlier attempts show that the influence of groups at the 2-, 4-, 5-

and 6-positions on hydride reduction is unclear, and that an electron-withdrawing moiety (CO_2Et , CN , etc.) in the 5-position appears to facilitate pyrimidine ring reduction.³⁹

In 1968, Mamaev and Gracheva⁴⁰ reported on the LiAlH_4 reduction of 4,6-diphenylpyrimidin-2(1H)-one. The yellow by-product, isolated from the reaction mixture was suggested to be 4,6-diphenyl-1,2-dihydropyrimidine, although they could not prepare it in an analytically pure form. By optimization of this reaction, we were able to attain this compound in a 78% yield.⁴¹



The LiAlH_4 reduction of pyrimidin-2-ones probably proceeds by a mechanism similar to that proposed for the reduction of amides, i.e. initial reduction of the amide group to the imine, followed by reduction of the $\text{C}=\text{N}$ double bond.

Evidence for the intermediacy of 4,6-diphenylpyrimidine can be taken from the fact that LiAlH_4 reduction of 4,6-diphenylpyrimidine indeed gave the 1,2-dihydropyrimidine. Analogously, 2-phenyl-1,6-dihydropyrimidine was prepared by LiAlH_4 reduction of 2-phenylpyrimidin-4(3H)-one and of 2-phenylpyrimidine.⁴¹ Quantitative preparation of a series of 4,6-dialkoxy (or alkylthio)-2,5-dihydropyrimidines was achieved by LiAlH_4 reduction of the corresponding pyrimidines, based on the knowledge that electron-donating groups at positions 4 and/or 6 of the pyrimidine ring tend to stabilize the 2,5-dihydro structure.⁴²

II.b.4 Miscellaneous Methods

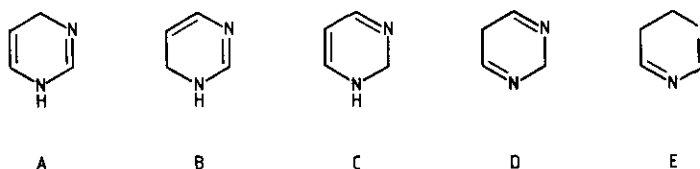
1,6-Dihydropyrimidines were isolated in the zinc, acetic acid catalyzed ring contraction of pyrimidines to pyrroles.⁴³

Girke⁴⁴ has recently shown that in the presence of trifluoroacetic acid, pyrimidine and 5-methylpyrimidine react with a number of active aromatic compounds to form stable 4-aryl-substituted dihydropyrimidinium salts, from which the dihydropyrimidine bases were obtained. Kashima *et al.* reported⁴⁵ preparation of *N*-substituted 1,2-, 1,4- and 1,6-dihydropyrimidines by the Raney nickel desulfurization of pyrimidine-2(1H)-thiones and their dihydro derivatives. Some

unusual cycloaddition and rearrangement reactions have also been shown to yield dihydropyrimidines.⁴⁶ Rearrangement of 1-benzyl-3,5-dimethylpyrazole in the presence of sodium amide was recently reported⁴⁷ to give 1,2-dihydropyrimidines.

III. STRUCTURE AND STABILITY

As indicated above the five possible two-dimensional structures for the isomeric dihydropyrimidines can be conveniently divided into two groups, namely the cyclic enamines (A-C), and the cyclic imines (D-E).

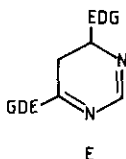
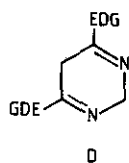


Most of the known dihydropyrimidines have either the 1,2- or the tautomeric 1,4- and 1,6-dihydro structures, probably because of π -conjugation existing in these entities. This structure is potentially homoaromatic as it contains a π -electron-delocalized entity, obeying the Huckel $4n+2$ rule. The degree of aromaticity of these compounds depends upon the orbital energies of the π -lone pair and the π -system, as well as, obviously, the degree of planarity of the molecule.

Gaussian-70 *ab initio* calculations of the energy of unsubstituted dihydropyrimidines yielded the following order of stability: $B > A > C > D > E$.⁴⁹

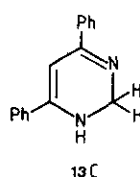
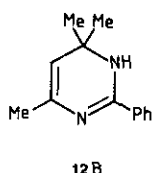
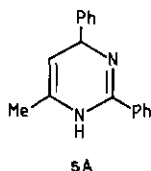
These results usually agree with the experimentally observed behavior of substituted dihydropyrimidine compounds. One can assume that less stable cyclic imines D-E will isomerize spontaneously via proton transfer (usually [1,3] or [1,5]) to the more stable cyclic enamines A-B-C, particularly where the energy difference between the imine and enamine is large. When energy difference is small, the isomers can exist in tautomeric equilibrium. Tautomerism can also be achieved by a proper selection of solvent and ring substituents.

By comparing all available data on chemical stability of cyclic imines and enamines one can conclude that, in general, the presence of electron-withdrawing substituents such as $-\text{COR}$, $-\text{CO}_2\text{R}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{SO}_2\text{R}$, etc. on the β -position of cyclic enamines, enhance their chemical stability. Similarly, introduction of electron-donating substituents such as $-\text{NR}_2$, $-\text{SR}$, $-\text{OR}$, etc. in the α or γ positions of usually unstable cyclic imines leads to enhanced chemical stability and enables easy isolation of these compounds. The only isolated 2,5-(D)^{37,38,42} and 4,5-(E)⁵⁰ dihydropyrimidines reported so far indeed contain such electron-donating groups.



EDG = Electron Donating Group

Recent X-ray examinations of the molecular structures of different dihydropyrimidine isomers were carried out in order to obtain unambiguous structural assignments for the conformation of these molecules in the solid state. Thus, an X-ray diffraction study on 4,6,6-trimethyl-2-phenyl-dihydropyrimidine (**12**) clearly showed⁵¹ the 1,6-dihydro structure **12B** in which similar to the 1,2-dihydropyridines¹, slight deviations from strict planarity was observed [N(1) and C(6) atom out of ring], the lone-pair electrons of N(1) undoubtedly conjugating with the double bonds.



The structure, geometry and conformation of solid 2,4-diphenyl-6-methyldihydropyrimidine (**5**) were also determined by X-ray diffraction.⁵² The analysis clearly shows that in the solid state, this compound has the 1,4-dihydro structure **5A**, with a nonplanar ring. Atoms N(1) and C(4) are out of the plane formed by the two double bonds [C(2)=N(3) and C(5)=C(6)] by about 0.10 and 0.25 Å, respectively, producing a ring with a flat-boat conformation. Particularly interesting data were obtained from the X-ray diffraction analysis of 4,6-diphenyl-1,2-dihydropyrimidine (**13C**) in which both C(2) [=47°] and C(5) [=18°] were out of the plane.⁵³ In addition, the distance between the two ring nitrogens of 2.8 Å is too great to permit formation of a monohomopyrazole exhibiting "homoaromaticity".

Attempts to verify the presence of "homoaromaticity" in solutions of 4,6-diphenyl-1,2-dihydropyrimidine (**13C**) by NMR measurements, as previously found for dihydrotetrazine⁵³, were not successful. One likely explanation for this might be significantly faster inversion flipping in the 1,2-dihydropyrimidine ring, which, to freeze, requires even lower experimental temperatures than those we investigated. A detailed analysis of ¹H and ¹³C NMR spectra of 1,2-dihydropyrimidinium salts was reported.^{24a} Authors assumed that the 2-position in these salts lies out of the plane of the conjugated portion of the molecule. However, attempts to observe possible

inversion in this system produced no change in the ^1H NMR spectrum down to -60°C .

It should be noted that the crystal structure of each of these compounds demonstrates the presence of an intermolecular $\text{NH}\cdots\text{N}$ hydrogen bonds. Molecular association through the $\text{NH}\cdots\text{N}$ hydrogen bond bridge is undoubtedly one of the major factors responsible for the fact that as a rule, 1,6-, 1,4- and 1,2-dihydropyrimidines unsubstituted at N(1) are solids, while N-substituted derivatives,⁴⁵ as well as 2,5-dihydropyrimidines,^{37,38,42} are liquids, or low melting solids.

Dihydropyrimidines in which the NH-hydrogen is available for intermolecular hydrogen bonding are soluble in polar and rather insoluble in nonpolar solvents (as CCl_4 , hexane, cyclohexane, etc.). When dihydropyrimidines are substituted in the position 1, these solubility characteristics are reversed.

Most of the synthesized 2,5-dihydropyrimidines are easily sublimed even at room temperature. Surprisingly, a low temperature X-ray diffraction study on the single crystals of 4,6-diethoxy-2,5-dihydropyrimidine showed that this molecule is completely planar.

IV. TAUTOMERISM

Existence of the five isomeric dihydropyrimidines (A-E) with different ground state energy and consequently different stabilities, gives rise to various isomerization processes, which are reversible or irreversible migrations of an entity from one site to another. The study of these isomerizations is still in its infancy. Thermal isomerizations, including hydrogen transfer in DHA, may be divided into those involving, formally, either [1,3]-hydrogen shift (amidinic and imine-enamine tautomerism) or [1,5]-hydrogen shift.

It is common practice to classify hydrogen migrations as either rearrangements or tautomerisms, the former being reserved for irreversible or slow processes, while the latter being used to describe fast, reversible exchanges.⁵⁴

IV.a Amidinic Tautomerism

Although prototropic tautomerism of compounds containing an amidine moiety has been studied extensively,⁵⁵ the data obtained on this type of equilibrium are rather qualitative and have not been explored systematically. The difficulties stem primarily from the common experience that proton transfer between electronegative atoms, such as nitrogen, is very fast.^{55,56}

The structure of amidinic compounds has usually been given in the literature as a presumed, predominant tautomer, without supporting evidence for a definitive structure. No data on tautomerism of dihydropyrimidines were available before our work.

Amidinic tautomerism in dihydropyrimidines was detected at first by spectral studies (NMR, IR, UV) of solutions of 6-methyl-2,4-diphenyl-dihydropyrimidines (5).¹² Particularly noteworthy is the observation of two individual tautomeric structures in the NMR spectra measured in aprotic dipolar solvents (DMSO, HMPA). However, when the IR and UV spectra of solid 5 were recorded in KBr, only one tautomer was present, but a definitive structural assignment could not be made from these data alone. X-ray diffraction, however, showed that in the crystalline state, compound 5 exists in the 1,4-dihydro form 5A.⁵² Thus, a combination of X-ray, NMR, IR and UV data are required to make definite spectroscopic assignments for each of the tautomers. Thus, the IR $\nu_{\max}$ band at 1700 cm^{-1} was attributed to the stretching mode of the C=C-NH-C=N fragment of 5A, whereas, the new band at 1645 cm^{-1} , which appears in solution, is due to the C=C-N=C-NH fragment of 5B.

Usefulness of IR and NMR data in assigning tautomer structure was further validated by our studies of dihydropyrimidine 12 using Silversmith's data.⁵⁷ We assigned it the 1,6-tautomeric form 12B, based on a reinvestigation of its IR band at 1652 cm^{-1} , which is similar to the IR spectra of 5B. This was later confirmed by X-ray analysis.⁵¹

The infrared spectra of a series of these compounds were of particular interest, since characteristic absorptions in the $1600\text{--}1700\text{ cm}^{-1}$ region seem to provide an excellent tool for differentiation between the tautomers. For a large number of newly prepared materials, it has been consistently observed that the C=C-NH-C=N band of the 1,4-tautomers appears $30\text{--}60\text{ cm}^{-1}$ higher in frequency than the corresponding band for the C=C-N=C-NH fragment of the 1,6-tautomer. The correctness of these assignments was confirmed recently by Kashima et al.⁴⁵ Appearance of two publications, in 1978-1979^{33,34} claiming that all attempts (even at -88°C) to obtain the NMR spectra of dihydropyrimidine tautomers, failed, stimulated further investigations aimed at identifying the factors enabling observation of such annular tautomerism. It was found⁵⁸, that in DMSO- d_6 solution tautomerism was affected by the following factors: dryness of the solvent, microconcentration of H^+ ions in solutions, paramagnetic impurities, and solute concentration.

Recalling that proton transfer between two heteroatoms is usually rapid (on the NMR time scale),^{55,56} it would be expected that the use of an aprotic dipolar solvent (DMSO, HMPA), should decrease the rate of tautomerism (due to strong intermolecular hydrogen-bonding with the solvent) and enable observation of the NMR signals of individual tautomers.

The fact that in CDCl_3 only "average" spectra were observed may be attributed both to a lack of hydrogen-bonding stabilization and to the minute amounts of acid which are usually present in this solvent. When the spectra were measured at low temperature on a dilute sample in purified CDCl_3 tautomerism was indeed observed.⁵⁸

Knowledge of the effects of solute and solvent purity on the rate of tautomerism made possible a systematic study of the temperature and concentration dependence of the rate of tautomerism.

Quantitative analysis of dynamic ^1H NMR data in specially purified CDCl_3 containing different concentrations of solute 5 enabled a determination of the effect of concentration on the rate.⁵⁹

At fixed temperature k_A can be written as:

$$k_A(T) = k_1(T) + k_2(T) [C]$$

where k_1 corresponds to a monomolecular reaction, while k_2 corresponds to a bimolecular path.

The kinetic parameters derived from these measurements are:

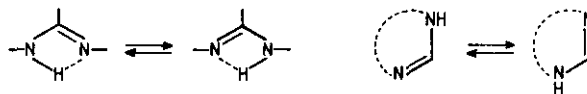
For k_1 :

$$k_1(300\text{K}) = 31 \pm 4 \text{ s}^{-1}; \Delta E^\ddagger = 4.5 \pm 0.6 \text{ kcal/mol}; \Delta H^\ddagger = 3.8 \pm 0.6 \text{ kcal/mol}; \Delta S^\ddagger = -43 \pm 3 \text{ cal/deg mol}$$

For k_2 :

$$k_2(300\text{K}) = (1.0 \pm 0.2) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}; \Delta E^\ddagger = 3.3 \pm 0.7 \text{ kcal/mol}; \Delta H^\ddagger = 2.7 \pm 0.7 \text{ kcal/mol}; \Delta S^\ddagger = -41 \pm 3 \text{ cal/deg mol}$$

This kinetic behavior suggests that two mechanisms are involved in the transformation between tautomers: one is first order with respect to concentration of 5, while the other is second order. The first-order reaction involves the solvent in a protolytic reaction, whereas the second-order reaction can be described as a proton exchange between two molecules of 5, resulting from bimolecular collision. This intermolecular mechanism of proton transfer in the cyclic amidine $5A \rightleftharpoons 5B$ is different from the intramolecular mechanism of proton transfer in acyclic amidines, being usually independent of the concentration of the solute.



In acyclic amidines rotation about the C-N bond can position the hydrogen on the $\text{N}(\text{sp}^3)$ near the lone pair of the $\text{N}(\text{sp}^2)$, leading to intramolecular hydrogen bonding that enables proton migration. In contrast, in cyclic amidines conformational changes of the ring system cannot produce intramolecular hydrogen bonding (because the hydrogen on the $\text{N}(\text{sp}^3)$ and the lone pair of the $\text{N}(\text{sp}^2)$ are oriented in different directions). In this case, only intermolecular proton transfer is possible. By understanding the factors influencing annular amidinic tautomerism in dihydropyrimidines, we were able to show that by suitable modification of the substituents or of the ring system itself, it was possible to increase or decrease the extent of delocalization of the lone pair of nitrogen electrons, with a concomitant increase or decrease in the rate of proton transfer.⁵⁶ The

delocalization effect was obtained by studying compounds in which phenyl groups at position 2 of dihydropyrimidines were replaced by methyl groups, or in which the conjugated C=C double bond was reduced to the corresponding tetrahydropyrimidines. Using both these approaches, the reduction of delocalization drastically enhanced hydrogen exchange. Having a phenyl instead of the methyl group at position 6 in dihydropyrimidine 5 decreased the rate of tautomerization, and separate signals for both isomers were detectable by ^1H and ^{13}C NMR in CDCl_3 at rather high concentrations (0.1 M) and at ambient temperature. Furthermore we observed that the steric environment of substituents adjacent to the amidinic fragment of dihydropyrimidines (particularly the bulkiness of substituents at the neighbouring sp^3 -hybridized carbon) also affects tautomeric exchange. Further investigations, however, are necessary to clarify the mechanisms. In particular ^{15}N NMR studies of annular tautomerism of dihydropyrimidines are of great interest since the chemical-shift data enable calculation of the electron density on the nitrogen. A correlation of the latter with the rates of tautomerism for a number of variously substituted dihydropyrimidines would be a critical test of the "delocalization hypothesis".

NMR-spectroscopy has been very useful to determine the amidinic tautomerism of the σ -adducts 10 and 11 formed between 5-nitropyrimidines and liquid ammonia.^{38a,60} In the C-2-adduct 10 ($\text{R} = \text{H}$) the carbon atoms at C-4 and C-6 have identical chemical shifts, indicating the existence of an equilibrium between both 1,2-dihydro compounds (10C). ^{15}N NMR spectroscopy of the σ -adduct 10 ($\text{R} = \text{H}$) also shows identical chemical shifts for both nitrogens confirming the tautomeric equilibrium 10C. ^{15}N NMR spectroscopy of the C-4 adduct 11 ($\text{R} = \text{H}$) has revealed that this C-4 adduct is exclusively present as the 1,4-dihydro tautomer 11A ($\text{R} = \text{H}$). No indication for the presence of tautomer 11B was found. The adducts 11 ($\text{R} = \text{SCH}_3$ and SO_2CH_3) however exist as a tautomeric mixture of the 1,4-dihydro (11A) and 3,4-dihydropyrimidine (11B).

IV.b Imine-enamine Tautomerism

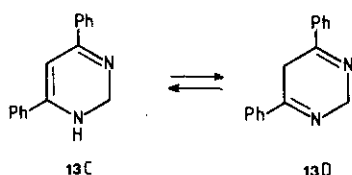
From structural consideration of the isomeric dihydropyrimidines two distinct types of imine-enamine tautomerism can be predicted, namely that between 4,5- (E) and 1,4-dihydropyrimidines (A) and between the 2,5- (D) and 1,2-isomers (C).



Imine-enamine tautomeric rearrangement was proposed as a possible mechanistic explanation of the

formation of dihydropyrimidines by condensation of α,β -unsaturated carbonyl compounds with amidines (see Scheme 2).

The equilibrium between 1,2- and 2,5-dihydropyrimidines depends mostly on the free-energy difference between the two isomers, solvent polarity and substituent effects on the dihydropyrimidine ring. Where free-energy difference is not overwhelmingly large, tautomeric equilibria can be observed experimentally for various dihydroazines. In the case of large energy differences, fast rearrangement to the thermodynamically more stable isomer occurs. This can explain the existence of imine-enamine tautomerism in 4,6-diphenyl-1,2-dihydropyrimidine. Where 1,2-dihydropyrimidine is present as a single tautomer, introduction of phenyl moieties at 4- and 6- position of 1,2-dihydropyrimidine enabled observation of two tautomeric forms, i.e. 4,6-diphenyl-1,2-(13C) and -2,5-dihydropyrimidine (13D) (using ^1H and ^{13}C NMR). The ratio of 13C to 13D (in CDCl_3) is 2:1, giving a ΔG° value of $0.41 \text{ Kcal/mol}^{-1}$ for the tautomerism in CDCl_3 . It should be noted that in $\text{DMSO}-d_6$, the equilibrium is completely shifted to the 1,2-dihydropyrimidine structure, the reason, obviously, is due to strong hydrogen bonding with the solvent, providing additional stabilization. (An analogous effect was observed in 1,6-dihydropyrazine.⁶¹)



Reduction of pyrimidines, containing electron-donating groups at position 4 and 6, with lithium aluminum hydride gives as single final product the 2,5-dihydropyrimidine derivatives, which are substantially more stable than the intermediate 1,2-dihydropyrimidines, undergoing imine-enamine tautomerism.⁴²

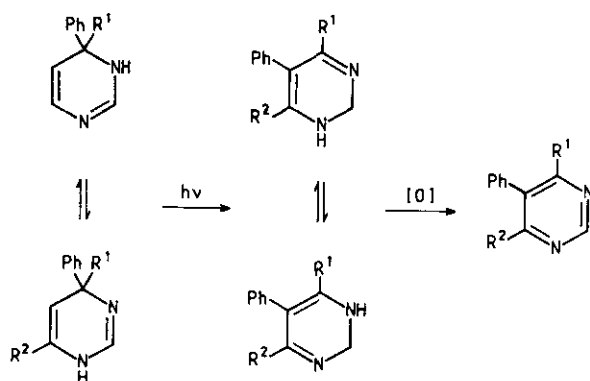
It was suggested that nonsymmetrically substituted 1,2-dihydropyrimidines undergo tautomeric equilibration via a [1,5]-hydrogen shift.²³ The same variety of tautomerism can be supposed for all N-unsubstituted 1,2-dihydropyrimidines. Suprafacial [1,5] sigmatropic hydrogen shift could also be responsible for the transformation of unstable 4,5-dihydropyrimidines to the thermodynamically more stable 1,6-dihydropyrimidines. (See Scheme 2).

Above-mentioned examples show that knowledge on migrations in dihydroazines is limited and that detailed research of these processes will certainly provide a deeper understanding of the problems of tautomerism and rearrangements as a whole, as well as of the energetics, reactivity and mechanisms of the formation of a variety of dihydroazines.

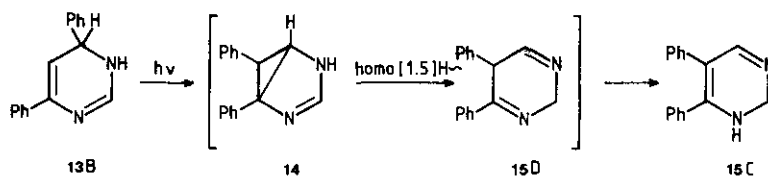
V. REARRANGEMENTS

V.a Di- π -methane Photochemical Rearrangements

Based on our own experience and data available in the literature, we can observe that interconversion between 1,4- 1,6- and 4,5-dihydropyrimidines and between 1,2- and 2,5-isomers is possible under thermal conditions. Thermal interconversion between the two groups is not observed, but photochemical rearrangement of 1,4- (and 1,6-) dihydropyrimidines to 1,2-isomers has been shown.

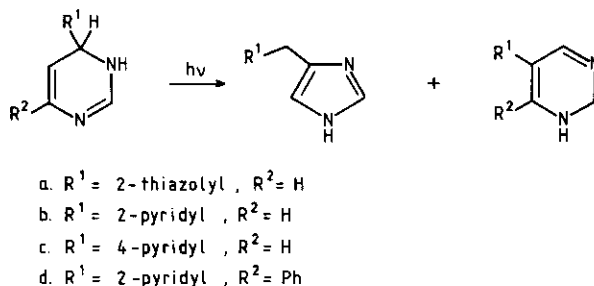


A di- π -methane mechanism was suggested for the photochemical isomerization of 4,6-diphenyl-1,6-dihydropyrimidine (**13B**) into 5,6-diphenyl-1,2-dihydropyrimidine (**15C**). It involves the formation of 2,4-diazabicyclo[3.1.0]hex-2(3)-ene (**14**) as an intermediate,^{34,35} subsequent opening of the three-membered ring in **14** with concomitant homo [1,5] hydrogen shift from nitrogen to carbon 2 yielding 4,5-diphenyl-2,5-dihydropyrimidine (**15D**), that undergoes an imine-enamine tautomerisation into **15C**.



Although the 2,5-dihydropyrimidines could neither be isolated nor detected by spectroscopic means, its intermediacy seems very likely as demonstrated by the fact that on irradiation of an N-1 deuterated analog of **13**, and oxidation of the photolysis a mixture of 4,5(=5,6)-diphenylpyrimidines was obtained containing 56.5% deuterium at C(2); this amount of deuterium is expected for a

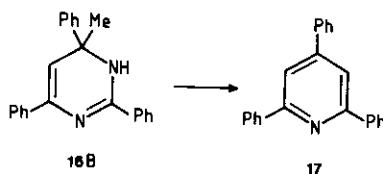
homo[1,5]-deuterium shift from nitrogen in 14 to C(2) in 15D. Moreover, recent ^1H and ^{13}C NMR spectroscopic investigations showed evidence for the formation of 6-(p-trifluoromethylphenyl) 2,4-diazabicyclo[3.1.0]hex-2(3)-ene in the photolysis of 4-(p-trifluoromethylphenyl) dihydropyrimidine.⁶² The isolation of the 1,2-dihydropyrimidine (15C) failed because of instability; therefore, evidence for its presence was only based on spectral and chemical data. It is of interest that by irradiation of 1,4(1,6)-dihydropyrimidines containing electron-withdrawing substituents at position 4, besides the di- π -methane rearrangement a photochemical ring contraction into imidazoles has been observed.⁶²



A 2-thiazolyl or 4-pyridyl group in position 4 causes an exclusive photoinduced ring contraction into an imidazole, while the 2-pyridyl substituent at C-4, however, leads to both an imidazole and a 5-substituted 1,2-dihydropyrimidine, whereas phenyl substitution in position 4 yields only derivatives of 1,2-dihydropyrimidine.

V.b Thermal Rearrangements

Very little work has been published on the thermolytic reactions of dihydropyrimidines. An interesting rearrangement was reported when 6-methyl-2,4,6-triphenyl-1,6-dihydropyrimidine (16B) was heated at 210°C. Ammonia was evolved and 2,4,6-triphenylpyridine (17) was obtained.⁶⁴ A plausible mechanism for this rearrangement has been proposed. Thermal rearrangements of dihydropyrimidines deserve further attention.



VI. REACTIVITY

The most important chemical property of dihydropyrimidines is their easy oxidation to the corresponding pyrimidines (via dehydrogenation, hydrogen transfer or disproportionation). However, although many such oxidations have been carried out, they were aimed at enabling identification of dihydropyrimidines from the pyrimidine formed, rather than to study the kinetics and mechanism of the oxidation reactions themselves.

It should be noted that the 1,4-dihydropyrimidine (5A) easily reduces some α,β -unsaturated ketones to saturated ketones (for example, chalcone, benzilideneacetylacetone, maleic anhydride, etc.), as well as some activated carbonyls, such as trifluoroacetone, pyruvic acid and phenyl glyoxylate. This important property of dihydropyrimidines needs further, through quantitative investigation.

The 2-amino-5-nitro-1,2-dihydropyrimidines (10C) and the tautomeric mixture of the 4-amino-5-nitro-1,4-dihydro- (11A) and 4-amino-5-nitro-3,4-dihydropyrimidine (11B) are very conveniently converted into the corresponding 2-amino-5-nitropyrimidines and 4-amino-5-nitropyrimidines respectively by oxidation with potassium permanganate in liquid ammonia at low temperature.^{38a} This method provides us with an efficient synthetic tool for introducing amino groups in heterocyclic system.⁶³

Tautomeric 1,4- and 1,6-dihydropyrimidines easily undergo nucleophilic addition and react with electrophilic reagents. For example, upon prolonged contact with moisture, the addition of water across the C=C bond with quantitative formation of 6-hydroxy-1,4,5,6-tetrahydropyrimidines, was observed. The products are identical to those obtained by the interaction of α,β -unsaturated carbonyl compounds with amidines and indicate the reversibility of the dehydration step in the course of dihydropyrimidine formation from 6-hydroxytetrahydropyrimidines. 4,6-Diphenyl-1,4(3,4)-dihydropyrimidine reacts with methyl iodide or methyl chloroformate into 4,6-diphenyl-3-methyl (or methoxycarbonyl)-3,4-dihydropyrimidine.⁹

VII. CONCLUSION

During our investigations of the chemistry of dihydropyrimidine systems, we have been rewarded by observations of surprising rearrangements, and several kinds of tautomeric transformations, as well as the amassing of new physicochemical data.

Further investigations of dihydropyrimidines should considerably expand our vistas in heterocyclic chemistry, as well as in biomedical research.

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