CHEMISTRY LETTERS, pp. 1773 - 1776, 1984.

PREPARATION AND IMINE-ENAMINE TAUTOMERISM OF 4,6-DIPHENYL-1,2-DIHYDROPYRIMIDINE[1)]

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4,6-Diphenyl-1,2-dihydropyrimidine was prepared by $LiAlH_4$ reduction of 4,6-diphenylpyrimidin-2(1H)-one or 4,6-diphenylpyrimidine. Using ^1H and ^{13}C NMR, it was shown that in $CDCl_3$ the product exists in tautomeric equilibrium with 4,6-diphenyl-2,5-dihydropyrimidines.

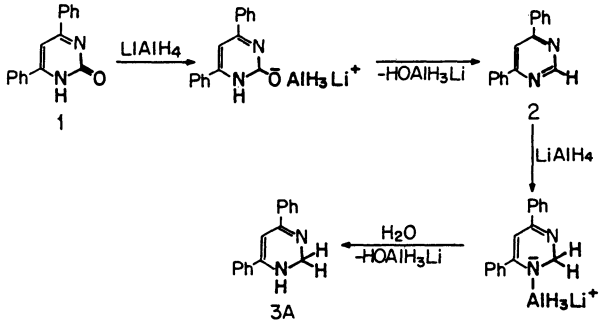
After successfully developing synthetic techniques for obtaining a variety of 1,4- and 1,6-dihydropyrimidines,[1,2)] as well as the observation in solution of amidinic tautomerism between the two,[3)] it was considered appropriate to examine the possibility of preparative synthesis of similarly N-unsubstituted 1,2-dihydro derivatives and to study their properties. Of particular interest would be the observation of thermally allowed [1,5]hydrogen rearrangement,[4)] homoaromaticity,[5)] or imine-emanine tautomerism, behaviours which might be predicted from related molecules.

To date, few reports on the formation of 1,2-dihydropyrimidines exist in the literature, and in those cases where a final product could be isolated and characterized, the material was either an N-substituted derivative, or else contained gem-disubstitution at position 2, situations that prevent the molecule from oxidation to the corresponding pyrimidine. Among the methods recorded are: a) $LiAlH_4$ reduction of pyrimidin-2(1H)-ones;[6)] b) multi-component condensations involving a β-dicarbonyl compound, a carbonyl-containing fragment and ammonia in the presence of ammonium salt[7)] (or modifications utilizing a β-dicarbonyl and a gem-diamine,[8)] or a diimine with a carbonylic reagent[9)]); c) Raney-Ni desulfurization of pyrimidin-2(1H)-thiones;[10)] d) electrochemical reduction of 4,6-dimethyl-2-phenylpyrimidine;[11)] e) rearrangement of 1-benzyl-3,5-diphenyl-pyrazoles in the presence of sodium amide[12)] and f) photochemical di-π-methane rearrangement of 1,4-dihydropyrimidines.[13)]

Because of the simplicity and convenience of $LiAlH_4$ reduction of amidines, we chose to examine the possibility of applying this procedure to preparation of 1,2-dihydropyrimidines. In 1968, Mamaev and Gracheva[6)] reported on the $LiAlH_4$ reduction of 4,6-diphenylpyrimidin-2(1H)-one. They suggested that a yellow by-product, isolated from the reaction mixture, was 4,6-diphenyl-1,2-dihydropyrimidine (3A), although their attempts to prepare an analytically pure sample of this material failed. Reinvestigation and optimization of this reaction enabled us to prepare

3A in 78% yield. This was achieved by addition with constant stirring of 5 g (20 mmol) 4,6-diphenylpyrimidin-2(1H)-one (1) to a suspension of 1.8g (45 mmol) $LiAlH_4$ in 50 ml dry ether and 100 ml dry dioxane. The ether was evaporated and the reaction mixture was boiled at 130 °C for ~ 15 h, monitoring hourly the formation of 3A by TLC (SiO_2, ethyl acetate). The reaction mixture slowly changed color to gray-green. The solvent was evaporated under reduced pressure, ether was added, and the unreacted $LiAlH_4$ was destroyed by the usual procedure. Etherial layer became intense yellow. After extraction, separation and drying ($MgSO_4$), the ether was evaporated and 4.5 g of brown-yellow solid was purified by column chromatography on SiO_2 (benzene-ethyl acetate). The yellow fraction was quickly evaporated at room temperature under reduced pressure. The yellow solid of 3A was recrystallized from hexane, mp 110-111 °C. Found: C, 82.05; H, 6.04%. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02%. λ_{max}^{EtOH} (ε): 207 nm (17200); 253 nm (15000); 377 nm (6390). Single crystals of 3A were grown by slow evaporation from hexane for X-ray diffraction study.[14]

$LiAlH_4$ reduction of pyrimidin-2-ones should proceed by a mechanism similar to that of amides, which involves reduction of the amide to the imine, followed by reduction of the available C=N double bond (see Scheme 1). If this is true, one



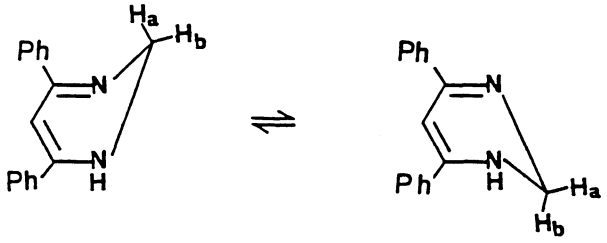
Scheme 1.

should also be able to obtain 3A by direct reduction of the corresponding 4,6-diphenylpyrimidine (2). Indeed, $LiAlH_4$ reduction in tetrahydrofuran converted 2 into 3A in 30-70% yield (depending on the reaction conditions). It should be noted that the reaction is very clean and aside from the end product, only the unreacted 2 could be detected in the reaction vessel. The reason for incomplete transformation of 2 is still unclear.

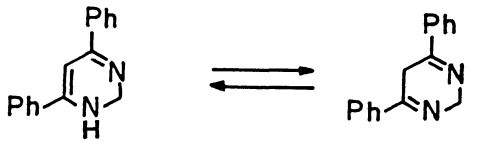
This reaction was extended to other derivatives. Thus, 2-phenyl-1,6-dihydropyrimidine (mp 120-121 °C) was prepared by $LiAlH_4$ reduction of 2-phenylpyrimidin-4-(3H)-one and 2-phenylpyrimidine. Undoubtedly, there is great potential in the reduction of pyrimidines with complex hydrides, and this approach should attract attention in the future.

Following successful preparation of 4,6-diphenyl-1,2-dihydropyrimidine (3A), an NMR study of the product was undertaken to examine the possibility of observing homoaromaticity in solutions, as previously reported for dihydrotetrazines.[15,16] To slow down conformational flipping and facilitate the observation of two signals for the protons on carbon 2, measurements were carried out at -60 °C (CD_3OD) and at -110 °C (CD_2Cl_2+freon-11). However, these conditions, similar to those used to

successfully detect homoaromaticity in dihydrotetrazines, failed. A similar failure to observe inversion in 1,2-dihydropyrimidinium salts has also been reported.[17]



One possible explanation would be a significantly more rapid inverting in the 1,2-dihydropyrimidine ring, than in dihydrotetrazines. Supporting this suggestion is X-ray structural data,[14] showing that the C(2) of 3A is much closer to the plane of the ring than is the corresponding carbon in dihydrotetrazine.



3A 3B

In $CDCl_3$, the NMR spectra of 4,6-diphenyl-1,2-dihydropyrimidine exhibited two new triplets at 3.56 (J=6.6 Hz) and 5.79 (J=6.6 Hz), which were assigned to 4,6-diphenyl-2,5-dihydropyrimidine (3B) (Fig. 1), the imine tautomeric form. The ratio of 3A to 3B is 2:1. This is the first observation of such imine-enamine tautomerism in dihydropyrimidines. It should be noted that in DMSO-d_6, equilibrium shifts entirely toward the 1,2-dihydropyrimidine (3A) due to strong intermolecular hydrogen bonding with the solvent. An analogous effect was observed in 1,2-dihydropyrazine.[18] This imine-enamine tautomerism is clearly observed in the ^{13}C NMR spectrum of 3A in $CDCl_3$ (Fig. 2). A simple calculation involving the concentrations of the two tautomers gives the value of ΔG° in this solvent as 0.41 kcal/mol.[19]

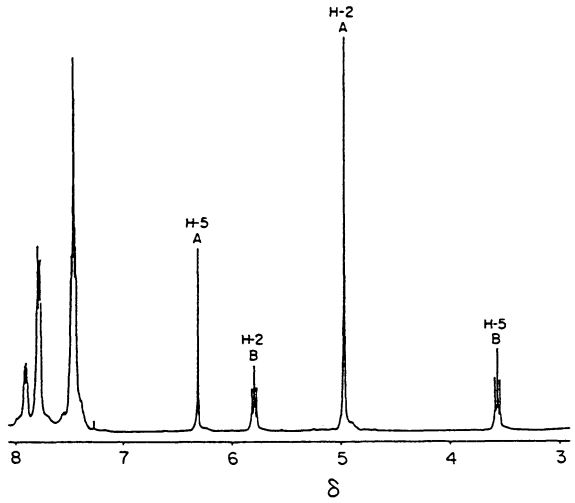


Fig. 1. 270 MHz ^1H NMR spectrum of 4,6-diphenyl-1,2-dihydropyrimidine (3A) in $CDCl_3$.

Moreover, since in the ^{13}C NMR spectra of 3A in $CDCl_3$, CD_2Cl_2, or CD_3OD the carbons at the 4 and 6 positions do not appear as separate signals, rapid tautomeric exchange of hydrogen atom between the two degenerate nitrogen atoms probably takes place ([1.5]hydrogen shift).

Imine-enamine tautomerism was previously observed in 3,6-diphenyl-1,2-dihydropyrazine[18] and in 3,6-diphenyl-4,5-dihydropyridazine solution.[20] The kinetics, the

mechanistic pathway and the influence of the positioning of nitrogens in the heterocyclic dihydroazine ring are under investigation. Certainly, it would be of great interest to determine whether a similar type of tautomerism exists in the analogues 5- and 7-membered heterocycles (e.g. 3,5-diphenylpyrazole and 5,7-diphenyl-2,3-dihydro-1,4-diazepine) which both possess the -NH-C=C-C=N fragment, but in which this variety of tautomerism has not been reported.

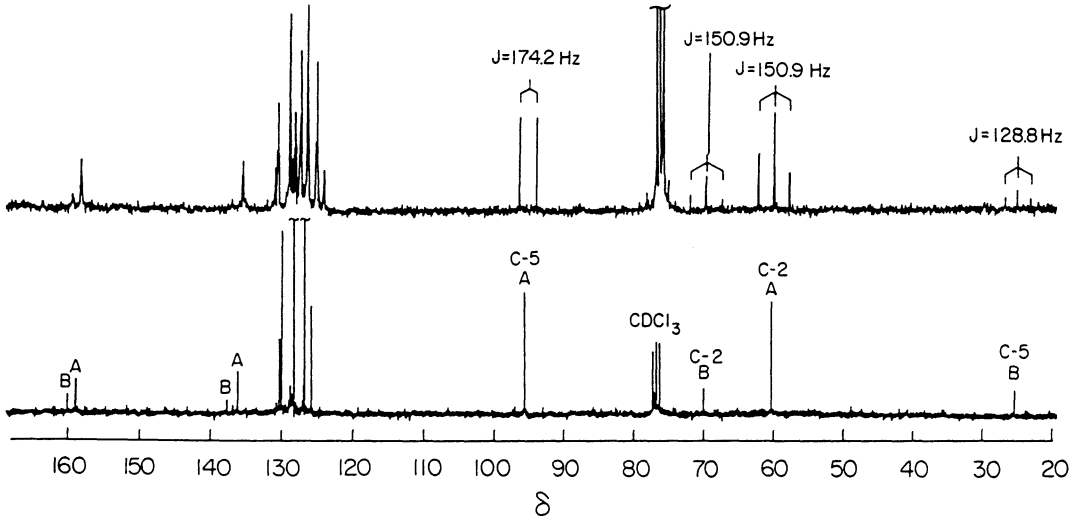


Fig. 2. 67.9 MHz ^{13}C NMR decoupled spectrum (bottom trace) and coupled spectrum (upper trace) of 4,6-diphenyl-1,2-dihydropyrimidine (3A) in $CDCl_3$.

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19) The difference in free energy, ΔG°, between the two tautomers can be calculated from the population of the two forms in solution: $\Delta G^{\circ} = -RT\ln K_T$, where $K_T = [A]/[B]$; R = 1.987 cal mol^{-1} K^{-1}; T = temp. K.
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(Received June 2, 1984)