Organic Reactions in the Aqueous Medium Part-V: Spectroscopic and Chromatographic Evidence for the Formation of Tautomeric Dihydropyridines in the Reactions of β-Diketo Compounds and Hexamethylene Tetramine (HMTA)

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Summary: Hexamethylene tetramine (HMTA) on reaction with β-diketo compounds (ethyl acetoacetate, acetylacetone and dimedone) yielded corresponding dihydropyridine derivatives in the aqueous medium. The formation of these tautomeric analogues has been established on the basis of spectroscopic and chromatographic evidence.

Introduction

In an earlier paper we reported a simple, convenient and economical route, especially for the formation of diethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (I) and 3,5-diacetyl-1, 4-dihydro-2,6-dimethyl pyridine (II) from the reaction of hexamethylene tetramine (HMTA) with ethyl acetoacetate and acetylacetone in the aqueous medium [1]. Their 60-MHz NMR spectra indicated expected absorptions for various protons, in conformity with literature [2], but with some additional peaks, initially mistaken for solvents of crystallization. Careful workup and purification failed to improve the spectra. However, critical examination of their 300-MHz NMR spectra manifested absorptions of their tautomeric analogues. According to literature survey evidence for such considerations has not been reported earlier in case of dihydropyridines [3] and is being presented in this manuscript for the first time.

Results and Discussion

The reactions of ethyl acetoacetate and acetylacetone with HMTA in the aqueous medium yielded corresponding dihydropyridines (I & II) (Fig. 1-a), which were correctly analysed for their elements and their molecular masses exactly corresponded to their molecular formulae. Their ^{1}H-NMR (60 MHz) spectra (Fig. 2 & 3), run in DMSO, were compared with the known spectra. The methyl (H_3C-CH_2-, -CH_3) and methylene groups (-CH_2-; CH_3CH_2-) signalled absorptions at 1.24 (triplet), 2.15 (singlet), 3.13 (singlet) and 4.15 (quartet) PPM respectively for the pure compound

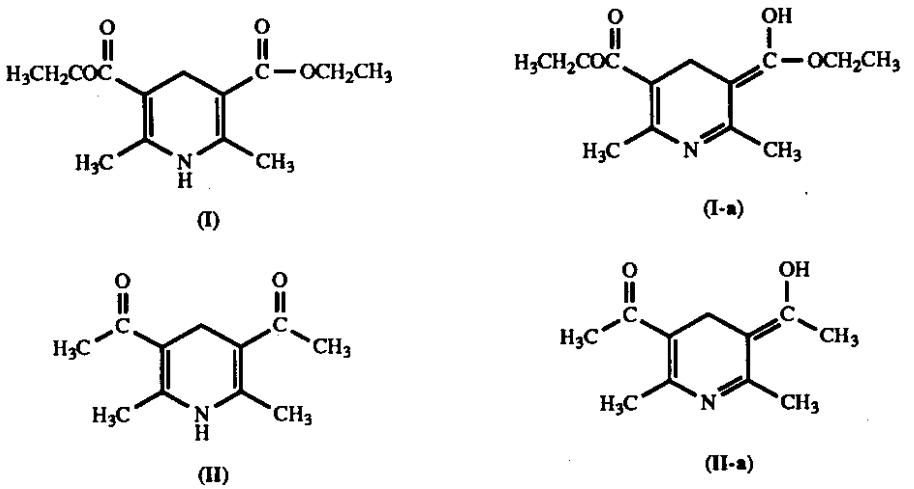

Fig. 1(a): Dihydropyridines and their tautomeric analogues.

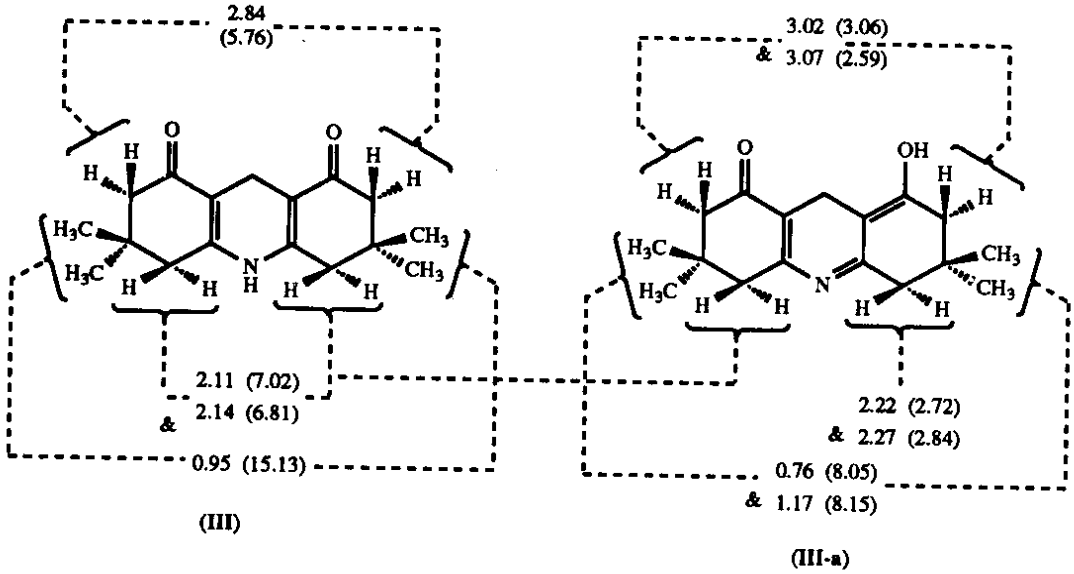

Fig. 1(b): Assignment of protons (PPM) in tautomeric analogues of dihydropyridines (III) and (III-a).

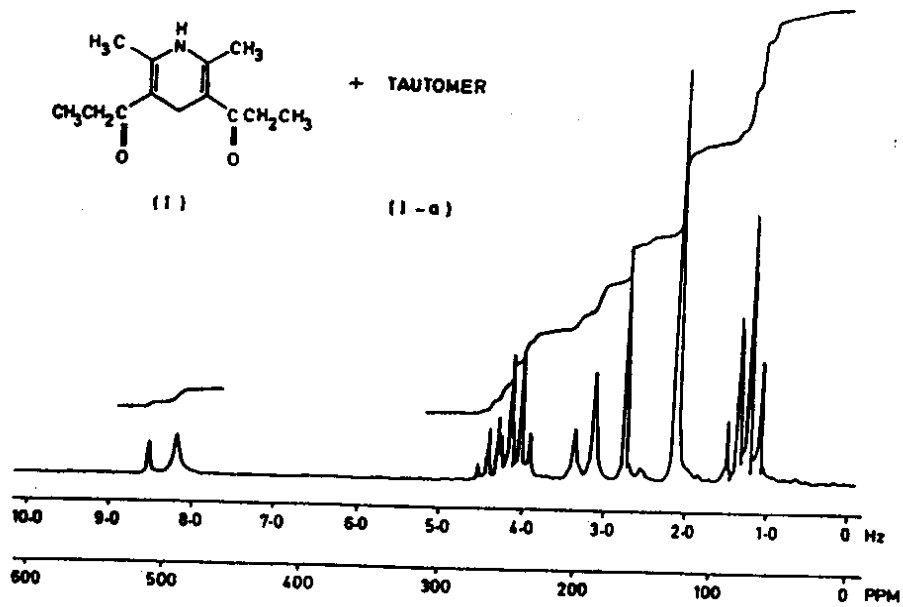

Fig. 2: ^{1}H-NMR (60 MHz) spectrum of dihydropyridines-(I) & (I-a) in DMSO.

(I) [2]. In case of authentic dihydropyridine-II, the singlets were observed at 2.11 (-CO-CH_3), 2.13 (-C-CH_3) and 3.25 ppm (-CH_2-) [2]. On the other hand, the spectra of our compounds had additional absorptions (see Fig. 2 & 3), which were initially mistaken for solvents of crystallization. Careful work and repeated purifications failed to improve these spectra which led to suggest that additional peaks were genuine and considered due to their tautomeric analogues. To verify this consideration, their HPLC was carried out. In this analysis both dihydropyridines (I & II), indicated two well separated peaks on the silica gel and the reversed phase columns respectively, as described in the experimental portion.

The ^{1}H and fully decoupled ^{13}C-NMR spectra (300-MHz) of (I & II) and their tautomeric analogues have been recorded and shown in Figs. 4-7. The assignment of various protons and ^{13}C absorptions have been collected in Table 1 and 2.

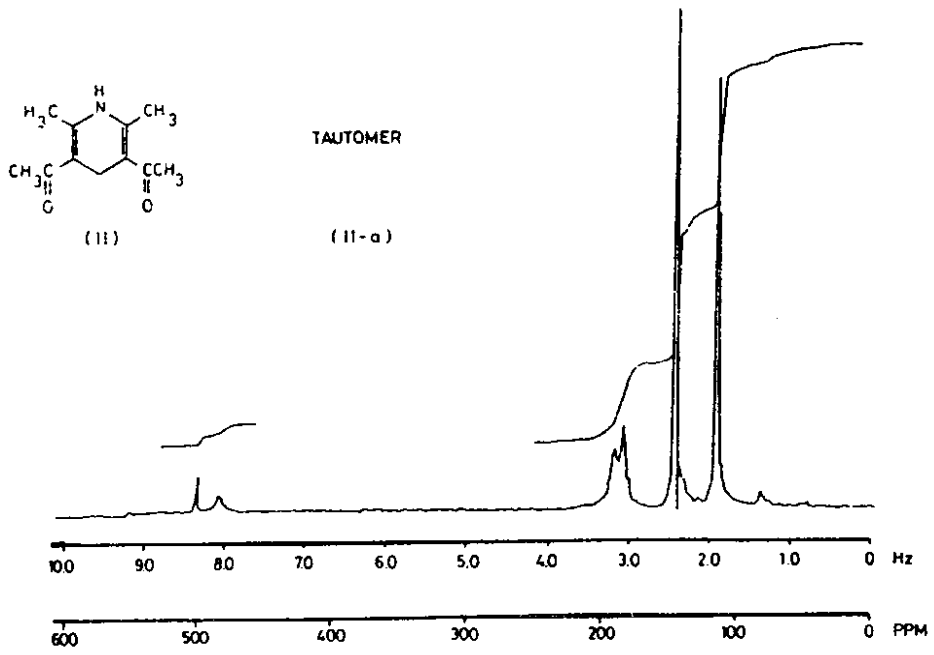

Fig. 3: ^{1}H-NMR (60 MHz) spectrum of dihydropyridines-(II) & (II-a) in DMSO.

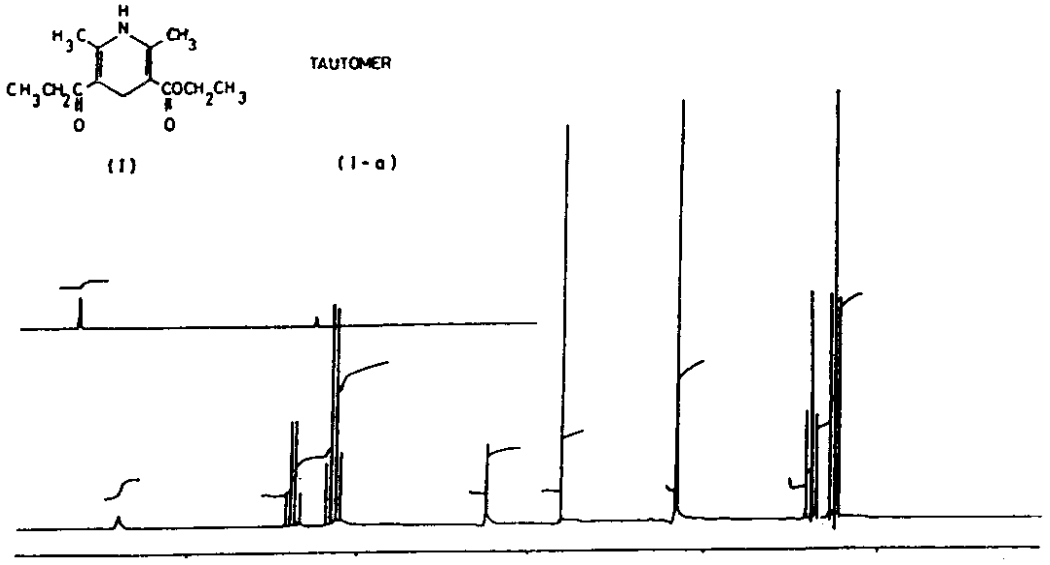

Fig. 4: ^{1}H-NMR (300 MHz) spectrum of dihydropyridines-(I) & (I-a) in $CDCl_3$.

The proton absorption of (I) are almost identical to literature values [2] cited earlier. This confirms the formation of this dihydropyridine. Based on the comparison of integral values of its protons with those of its tautomeric analogues the ratio of (I) and (I-a) approximates to 2:1 (66 % and 33%) respectively (Table 1-a). The fully decoupled ^{13}C-NMR absorption of (I) and (I-a) as shown in Table-1b have been tentatively assigned on the basis of their electronic environments. These values also support the formation of their tautomeric analogues.

The values of various proton absorptions of (II) as given in Table 2a also agree with the literature values of this dihydropyridine [2]

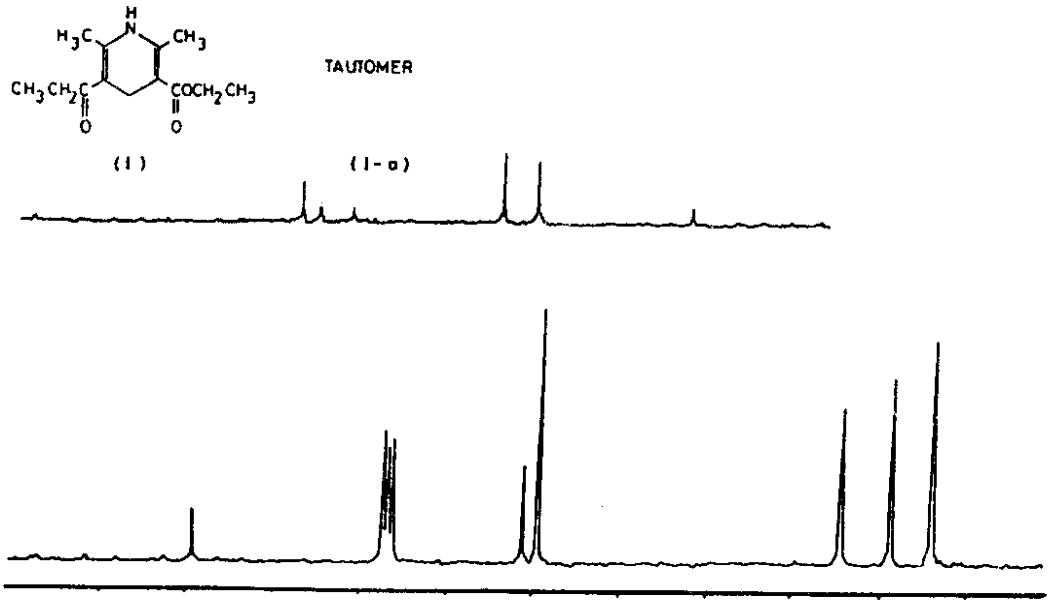

Fig. 5: Fully decoupled ^{13}C-NMR (300 MHz) spectrum of dihydropyridines- (I) & (I-a) in $CDCl_3$: CD_3OD (9:1).

Table -1

Assignment of various proton absorptions of dihydropyridine-(I) and its tautomeric analgue-(I-a) in $CDCl_3$

		NH	$-\overline{C}H_2CH_3$	$\overline{C}H_2$	CH_3	$-CH_2\overline{C}H_3$
(I)	PPM	5.39	4.14(q)(J : 7.1)	3.24(s)	2.16(s)	1.26(t)(J : 7.1)
	(Integ)	(2.7)	(11.0)	(6.4)	(17.2)	(16.6)
		OH	$-\overline{C}H_2CH_3$	$\overline{C}H_2$	N	$-CH_2\overline{C}H_3$
(I-a)	PPM	8.65	4.37(q)(J : 7.1)	3.24(s)	2.82(s)	1.39(t)(J : 7.1)
	(Integ)	(0.95)	(5.3)	(6.4)	(8.2)	(7.9)

Assignment of various ^{13}C- absorptions (PPM) of dihydropyridine-(I) and its tautomeric analgue-(I-a)

(I)	PPM	167.97	144.79	140.79	59.48	24.69	18.93	14.28
(I-a)	PPM	165.88	162.100	122.99	99.39	61.26	24.69	18.93	14.12

Table -II

a) Assignment of various proton absorptions of dihydropyridine-(II) and its tautomeric analgue-(II-a) in $CDCl_3$: CD_3OD (9:1)

		NH	CH_2	N CH_3	O CH_3
(II)	PPM	4.24	3.14 (s)	1.98 (s)	1.92 (s)
	(Integ)	(8.61)*	(6.78)	(18.17)	(19.53)
		OH	CH_2	N CH_3	OH CH_3
(II-a)	PPM	8.13	3.14 (s)	2.50 (s)	2.42 (s)
	(Integ)	(1.10)	(6.78)*	(6.85)	(6.42)

*includes residual CH_3OH

b) Assignment of various ^{13}C- absorptions (PPM) of dihydropyridine-(II) and its tautomeric analgue-(II-a)

(II)	198.75	146.25	137.86	29.31	26.61	18.63
(II-a)	159.83	130.00	107.97	28.79	23.89

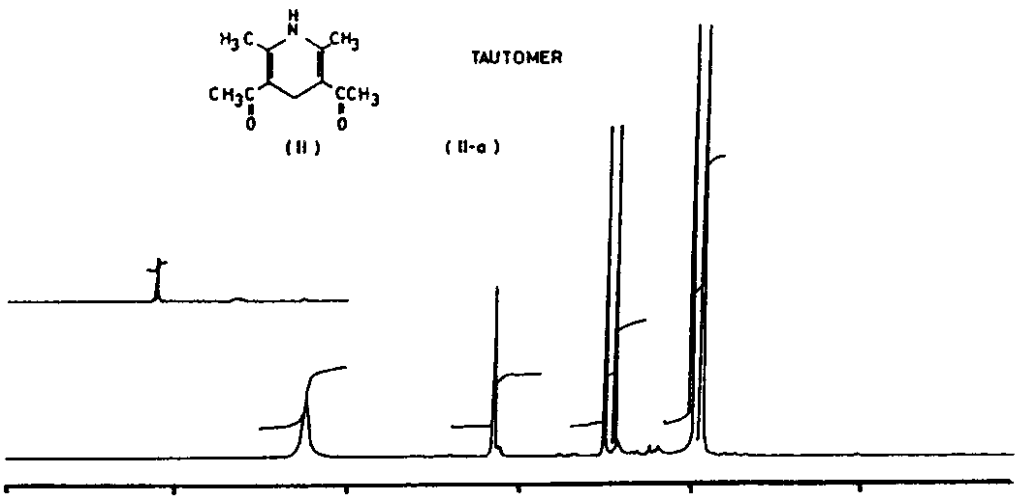

Fig. 6: ^1H-NMR (300 MHz) spectrum of dihydropyridines-(II) & (II-a) in $CDCl_3$: CD_3OD (9:1).

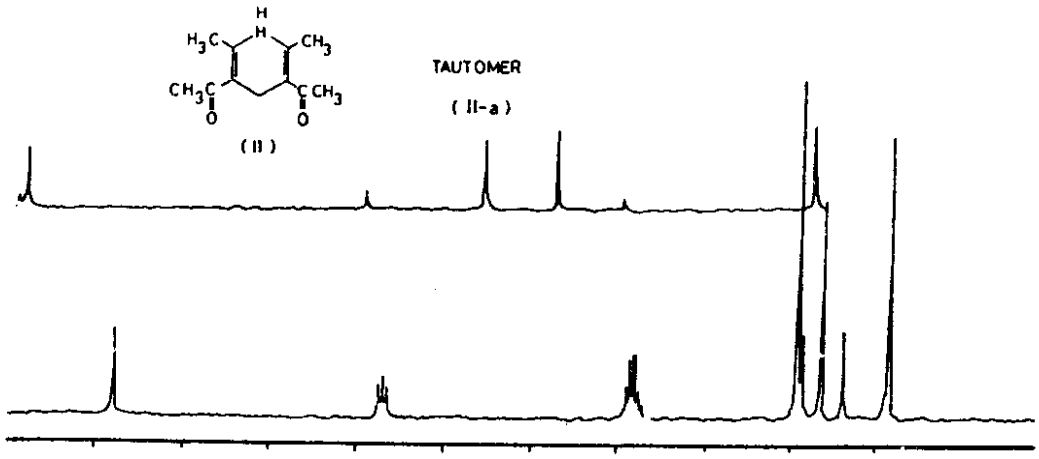

Fig. 7: Fully decoupled ^{13}C-NMR (300 MHz) spectrum of dihydropyridines- (II) & (II-a) in $CDCl_3$: CD_3OD (9:1).

described earlier. The small difference, if any, between various values of particular protons may be attributed to solvation in different solvents in which their spectra were run. The integral values of various protons for (II) and (II-a) as shown in Table 2a suggest that these tautomeric analogues are forming roughly in the ratio 3:1 (75% and 25%) in the reaction under consideration. The tautomeric nature of (II) and (II-a) is further manifested from their ^{13}C- absorptions as shown in Table 2b. The tentative assignment of different carbons has been made on the basis of electronic consideration. Similar behaviour of the reaction product of dimedone and HMTA has been observed (Fig. 8: 300-MHz ^{1}H-NMR). In the light of electronic environments the tentative assignment of various protons (ppm) of the tautomeric analogues (III and III-a) of the dihydropyridines of dimedone obtained has been indicated in Fig. 1b, where the values in brackets correspond to their integral. It may be inferred from these values that the formation of these analogues takes place approximately in equal ratio.

Thus, it may be concluded that β-diketo compound (ethyl acetoacetate, acetylacetone and dimedone) on reaction with HMTA in the aqueous medium yield a mixture of respective tautomeric derivatives of their dihydropyridines. According to our information, formation of prototropic tautomers of such heterocyclic compounds has not been reported earlier [3].

Reaction scheme

The dihydropyridines (I) and (II) are prepared in accordance with the well known procedure and reaction scheme of their formation has also been proposed [8]. On the other hand, current study reveals that these β-diketones on reaction with HMTA yield a tautomeric mixture of the corresponding dihydropyridines. This may be rationalised by the reaction of a conjugated imine (V), *in situ*, with both keto and enolic form of the β-diketo compound. Thus, ethyl acetoacetate and HMTA are proposed to react to yield dihydropyridine (I) and (1-a). The other β-diketo compounds are likely to follow similar route for the formation of their tautomeric analogues (Fig. 9).

Experimental

The dihydropyridines (I, II and III) were prepared from β-diketo compounds (ethyl acetoacetate, acetylacetone and dimedone) and HMTA in accordance with our reported procedure [1]. Their 60-MHz NMR spectra were run on Hitachi Model R-24B in deuterated DMSO. Their ^{1}H and fully decoupled ^{13}C-NMR spectra (300 MHz) were also recorded in $CCDl_3$ (for I and III) and $CDCl_3$: CD_3OD (9:1) (for II), and their molecular masses determined at the Department of Chemistry, University of Sherbrocke, Canada. Their synthetic details are as follows:

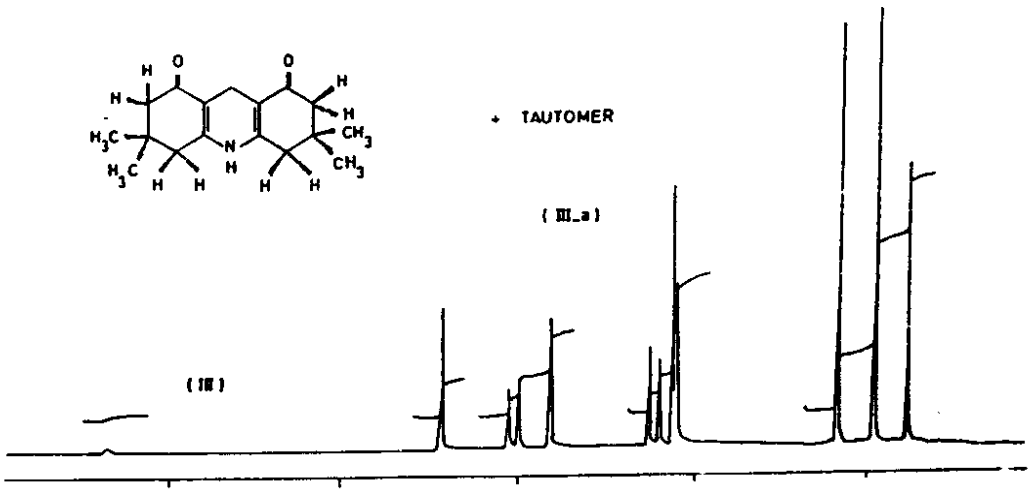

Fig. 8: ^{1}H-NMR (300 MHz) spectrum of dihydropyridines-(III) & (III-a) in $CDCl_3$

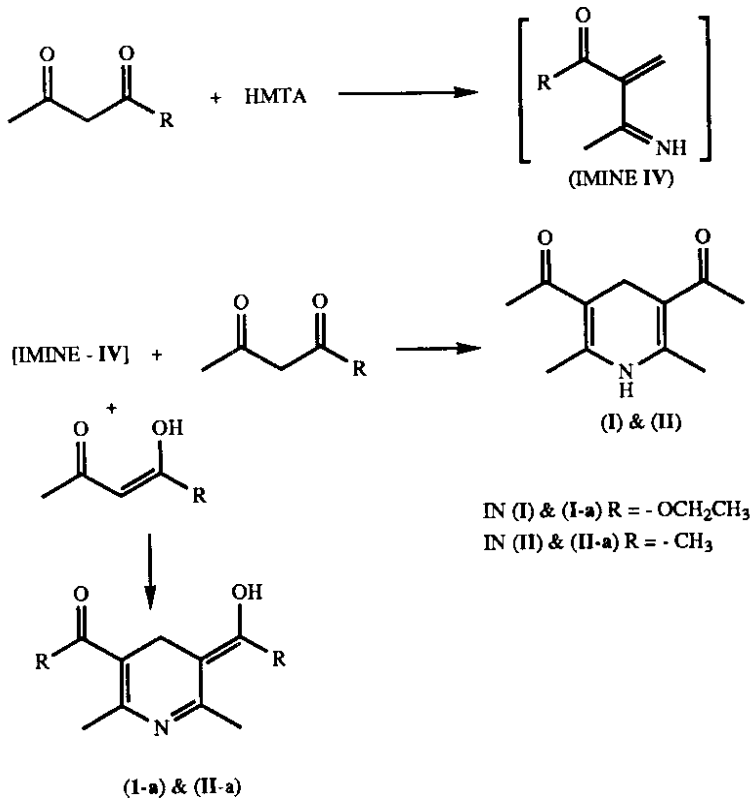

Fig. 9: Proposed route for the formation of dihydropyridines and their tautomeric analogues.

Diethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicar boxylate (I) and its tautomeric analogue (I-b)

To hexamethylene tetramine (2.33 g; 0.0166 mol) dissolved in water (25 mL) was gradually added ethyl acetoacetate (6.50 g; 0.05 mol) and shaken thoroughly to dissolve. The volume of the reaction mixture was made up to 50 mL by addition of water. It was allowed to dissolve at room temperature (30 ± 3°) with occasional shaking. After 5 days yellow fluffy compound (4.71 g; 75%) was obtained, which on crystallization from ethanol afforded yellow crystals, m.p. 178-183°; lit. [4,5] m.p. 181-183°. Its mass spectrum indicated

molecular ion at m/z 253 corresponding to its molecular formula, $C_{13}H_{19}NO_4$ (calculated: C, 61.66; H, 7.51; N, 5.53%. Found: C, 61.64; H, 7.53; N, 5.50%). ^1H and ^{13}C-NMR spectra have been described and discussed later.

3,5-Diacetyl-1,4-dihydro-2,6-dimethylpyridine(II) and its tautomeric analogue (II-b)

Accetylacetone (2,4-pentanedione) (5.0 g; 0.05 mol) was slowly added to a solution of hexamethylene tetramine (0.875 g; 0.00625 mol) dissolved in water (25 mL) and shaken vigorously until homogenous. The volume of the reaction mixture was then made upto 50 mL and shaken gently till a clear solution was obtained. The reaction mixture was kept at room temperature (30 ± 3°) for 3 days to yield yellow short needles (2.56 g; 53%), which on crystallization from ethanol yielded bright yellow fluffy needles melting at 196-198°C with decomposition; lit. [6] m.p. 198°. Its molecular ion (m/z 193) agreed with its formula, $C_{11}H_{15}NO_2$ (calculated: C, 68.39; H, 7.77; N, 7.25%. Found C, 68.41; H, 7.78; N, 7.22 %) ^1H and ^{13}C-NMR spectra have been described and discussed in "results and discussion".

1,8-Dioxo-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine (III) and its tautomeric analogue (III-b)

Dimedone(5,5-dimethyl-1,3-cyclohexanedione) (560 mg; 0.04 mol) and hexamethylene tetramine (140 mg; 0.001 mol) were dissolved in 12 mL of 1,4-dioxane-water (2:1). The mixture was refluxed gently for 1-2 hrs., diluted with water (5 mL) and allowed to stand at room temperature (13 ± 2°) . Pale yellow compound (242 mg; 44%) precipitated after one day was purified by recrystallization from ethanol to yield white needles, m.p. 263-267° (decomp.), lit. [7] m.p. 267°. Its combustion analysis agreed with its molecular formula, $C_{17}H_{23}NO_2$ (calculated: C, 74.73; H, 8.43; N, 5.13%. Found: C, 74.42; H, 8.46; N, 5.10%). Proton NMR spectrum has been shown and discussed later.

The HPLC of compound I and II were carried out on Hitachi (LC 638-30 low pressure ternary gradient system) instrument. A UV-VIS (LD/Milton Roy variable wavelength detector) was employed for the detection of the peaks. The chromatographs were recorded on Hitachi (# 833) data processor. Reversed phase (4.00 ID x 250 mm packed with Licrosorb RP-18, 10 µm, Merck) and normal phase (4.00 ID x 250 mm) packed with Licrosorb Si 60, 5 µm, Merck) columns were used for the separation of the compounds. Flow rate in each case was 1.00 ml/min and wave length was fixed at 254 nm. The mobile phase with the reversed phase column was acetonitrile: water (1:1 v/v) and with the normal phase chloroform: *n*-hexane: TEA (80:20:0.5 v/v).

The dihydropyridine (I) got resolved on the silica gel column and showed two well separated peaks having 3.67 and 10.59 min as their retention times. Whereas, the dihydropyridine (II) eluted as such having a retention time of 7.63 min. On the other hand, the latter (II) got resolved on the reversed phase column and inciated two well separated peaks corresponding to 2.66 and 3.4 min as their retention times. However, on this column the former (I) eluted as such corresponding to a retention time of 10.34 min.

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