Tetrahedron Letters Vol. 21, pp 2105 - 2108 0040-4039/80/0515-2105$02.00/0

SYNTHESIS AND NMR SPECTROSCOPIC PROPERTIES OF SOME METHYL-SUBSTITUTED 1-METHYL-1,4-DIHYDROPYRIDINES

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Abstract: The synthesis and NMR spectroscopic properties of some methyl-substituted 1-methyl-1,4-dihydropyridines are described.

1,4-Dihydropyridines are of utmost importance in bio-catalytic systems, particularly NADH which is involved in biological oxidation-reduction[1]. Simple dihydropyridines, however, have not been extensively studied due to their susceptibility to oxidation- and addition reactions and because of the lack of convenient methods for their preparation. Since we are interested in hydrogen-transfer reactions promoted by divalent metal ions coordinated to the annular nitrogen atom of 1,4-dihydropyridines[2], we tried to synthesize some simple 1-methyl-1,4-dihydropyridines by the metal-ammonia reduction of methylpyridines as described by Birch and Karakhanov[3]. However, we were unable to reproduce the reported yields and purities of the 1,4-dihydropyridines. Mixtures containing unreduced starting material, the desired 1,4-dihydropyridine and products resulting from further reduction were obtained. Since these compounds are difficult to separate we found the procedure not very satisfactory. In this communication we wish to report a modified method of reduction by which methyl-substituted 1-methyl-1,4-dihydropyridines can be prepared in higher yield and purity. Included as well are previously unreported NMR data, essential to the characterization of the compounds.

A solution of N-methylpyridinium salt (0.5 mol) - prepared from the selected pyridine derivative and methyl iodide - and 2 equivalents of ethanol in liquid ammonia (1 l) at ca. -33° C, was treated with lithium (2 equiv.). The metal rapidly dissolved and the colour of the reaction mixture changed gradually from orange-red to yellow-white. After the complete disappearance of the lithium, water (2 equiv.) was added in order to prevent coordination of the formed dihydropyridine to the alkali salt, and the ammonia was allowed to evaporate. The residue was handled further in an oxygen-free nitrogen atmosphere. After extractions with pentane or hexane and evaporation of the combined hydrocarbon layers (10° C, 15 mm), the residue was evaporated in vacuo (25° C, 0.1 mm) and the volatile material collected in a cold trap. In this way, without further purification, the 1-methyl-1,4-dihydropyridine derivatives were obtained in 80-90% yield and over 85% purity. The best results (over 95% purity) were obtained for 1,2-dimethyl-1,4-dihydropyridine and 1,2,6-trimethyl-1,4-dihydropyridine. All 1-methyl-1,4-dihydropyridines described here are air-sensitive colourless liquids, which can be stored at -20° C without appreciable deterioration.

The main difference between this synthesis of 1-methyl-1,4-dihydropyridines and the original procedure of Birch and Karakhanov is the a priori formation of the N-CH_3 bond. In the latter method this bond is formed by quenching the reaction mixture [pyridine derivative, ethanol (2 equiv.) and lithium (3 equiv.) in ammonia] with methyl iodide. The a posteriori formation of the N-CH_3 bond also necessitates the use of an extra equivalent of lithium in order to maintain the nitrogen in its anion form during reaction. This excess of lithium might well be responsible for the formation of tetrahydro- and hexahydropyridine side products.

The ^1H NMR and ^{13}C NMR data of the methyl-substituted 1-methyl-1,4-dihydropyridines are presented in tables 1-3. The most striking feature in these compounds is the six-bond ^1H-^1H coupling between the N-CH_3 protons and the 4-proton(s) of the dihydropyridine ring. Similar couplings were also found in other 1-methyl-1,4-dihydropyridines, e.g. in 1-methyl-N,N-dimethyl-1,4-dihydronicotinamide (^6J=0.57 Hz) and 1-methyl-3-cyano-1,4-dihydropyridine (^6J=0.63 Hz). These longe-range couplings probably arise from hyperconjugation between the π-electron system and the electrons in the C-H σ bonds. The ring system of the molecule is expected to be planar on the basis of X-ray studies of 1,4-dihydronicotinamide[4] and theoretical considerations[5,6]. The geometry of the molecule, therefore, does not allow a so-called "through-space" coupling, since in that case the dihydropyridine ring should be in a boat conformation.

It is a characteristic feature of longe-range coupling constants in unsaturated hydrocarbons that the magnitude of the coupling does not decrease strongly as the number of bonds between the hydrogen nuclei increases[7]. This is consistent with the mechanism of $\sigma-\pi$ interaction proposed by Karplus[8], which predicts that methyl-substitution should not change the magnitude of these coupling constants. To check whether this mechanism is operative in our compounds, we determined the ^5J values in 1,4-dihydropyridine (^5J=0.19 Hz) and 1,4-dihydro-N,N-dimethylnicotinamide ($^5J \approx 0$ Hz). Surprisingly, the values of these coupling constants are much lower than expected. To clarify these results, a diagrammatic representation of the possible interactions involved in the longe-range coupling present in 1-methyl-1,4-dihydropyridine, is given in figure 1.

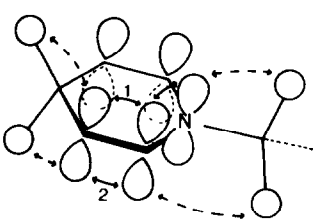

Figure 1. Longe-range hydrogen nuclear coupling in 1-methyl-1,4-dihydropyridines; (———) indicates the π-bond pairing of the electrons and (— — —) the $\sigma-\pi$ interaction of electrons.

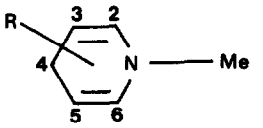

Table 1. ^{1}H NMR chemical shifts[a] (in ppm rel. to TMS) of some methyl-substituted 1-methyl-1,4-dihydropyridines.

substituent (R)	H_2	H_3	H_4	H_5	H_6	H_{Me}	H_R
none	5.62	4.30	2.90	4.30	5.62	2.72	
2-methyl		4.15	2.90	4.27	5.63	2.77	1.68
3-methyl	5.45		2.81	4.34	5.65	2.68	1.47
4-methyl	5.66	4.31	3.06	4.31	5.66	2.74	1.00
2,6-dimethyl		4.24	2.85	4.24		2.82	1.74

Table 2. Proton-proton coupling constants (in Hz) of (methyl-substituted) 1-methyl-1,4-dihydropyridines.

1-methyl-1,4-dihydropyridine

J	2	3	Me(1)
3	7.74		
4	1.37	3.16	0.6
5	0.24	2.27	
6	1.67		

1,2-dimethyl-1,4-dihydropyridine

J	4	5	6	Me(1)	Me(2)
3	3.07	2.20			1.20
4		3.17	1.35	0.71	1.38
5			7.64		

1,3-dimethyl-1,4-dihydropyridine

J	4	6	Me(1)
2	1.35	1.44	
4		1.44	0.57
5	3.10	7.63	

1,4-dimethyl-1,4-dihydropyridine

J	2	3	Me(1)	Me(4)
3	7.78			
4	1.05	3.38	0.53	6.42
5	0.17	2.47		
6	1.74			

Table 3. ^{13}C NMR chemical shifts[a] (in ppm rel. to TMS) of some methyl-substituted 1-methyl-1,4-dihydropyridines.

substituent (R)	C_2	C_3	C_4	C_5	C_6	C_{Me}	C_R
none	131.8	96.9	21.8	96.9	131.8	39.9	
2-methyl	136.6	95.3[b]	23.6	97.2[b]	133.4	37.0	19.0
3-methyl	126.0	105.3	27.5	95.6	131.0	39.5	19.9
4-methyl	129.9	102.9	26.5	102.9	129.9	39.7	26.3
2,6-dimethyl	137.3	96.4	23.7	96.4	137.3	31.9	19.6

[a] Solutions in $CDCl_3$; [b] Assignments may be reversed

$^{6}J_{H,H'}$ receives contributions from the two interaction paths indicated. In contrast, in 1,4-dihydropyridine only one interaction path, viz. that involving the nitrogen π orbital, is possible due to the in-plane orientation of the N-H proton. We believe, therefore, that the observed difference in the longe-range coupling constants, $^{5}J_{H,H'}$ and $^{6}J_{H,H'}$, is caused by the different modes of interaction between the protons H and H'.

Upon coordination of the (methyl-substituted) 1-methyl-1,4-dihydropyridines to divalent metal ions, $^{6}J_{H,H'}$ disappears. Participation of the nitrogen lone-pair in coordination and a change in the geometry of the 1,4-dihydropyridine, may be responsible for this effect. The zinc-bound 1-methyl-1,4-dihydropyridines are much more reactive in hydrogen-transfer reactions to unactivated carbonyl-containing substrates than free dihydropyridines. Studies related to the nature of these NADH model reactions and the complexes involved, are currently in progress[9].

Acknowledgement

This investigation was supported by the Netherlands Foundation for Chemical Research (S.O.N.) with financial aid from the Netherlands Organization for the Advancement of Pure Research (Z.W.O.).

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(Received in UK 17 March 1980)