

INTERPRETATION OF ^{13}C NMR CHEMICAL SHIFTS OF HANTZSCH'S PYRIDINES AND 1,4-DIHYDROPYRIDINES

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Received May 18th, 1983

^1H and ^{13}C NMR spectra of twelve 1,4-dihydropyridines *I* and twelve corresponding pyridine derivatives *II* have been measured in hexadeuteriodimethyl sulphoxide and interpreted. Correlation equations are given for the chemical shifts of the atoms in the heterocyclic rings of the two series of compounds.

In the context of studies¹ of the solution conformation of pharmaceutically interesting 1,4-dihydropyridine derivatives by means of dipole moments, we synthesized a series of Hantzsch's 1,4-dihydropyridines *I*. Literature² gives the ^{13}C NMR data only for a series of diethyl esters type *I* (R = substituted phenyl), and, therefore, we decided to complete this information and publish the ^{13}C NMR spectra of twelve 1,4-dihydropyridines *I* and the corresponding pyridine derivatives *II*.

EXPERIMENTAL

The 1,4-dihydropyridines *I* were prepared by the Hantzsch synthesis³ and oxidized to the pyridine derivatives *II* with sodium nitrite in acetic acid³. The newly prepared compounds were identified by elemental analysis: Compound *Ilg*, m.p. 127–130°C; for $\text{C}_{17}\text{H}_{17}\text{NO}_4$ (299.3) calculated: 68.21% C, 5.79% H, 4.68% N; found: 68.21% C, 5.94% H, 4.58% N. Compound *Iik*, m.p. 143–145°C; for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$ (312.3) calculated: 65.38% C, 5.13% H, 8.97% N; found: 65.35% C, 5.21% H, 8.74% N. Compound *Iim*, m.p. 103–105°C; for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_6$ (344.4) calculated: 59.30% C, 4.65% H, 8.14% N; found: 59.25% C, 4.72% H, 8.03% N. Compound *Iin*, m.p. 71 to 72°C; for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_6$ (372.4) calculated: 61.28% C, 5.41% H, 7.52% N; found: 61.21% C, 5.51% H, 7.19% N. The other compounds prepared were characterized by their melting points which agreed with the literature data^{4–15}. All the NMR measurements were carried out in hexadeuteriodimethyl sulphoxide with tetramethyl silane as the internal standard. The ^1H NMR spectra of the compounds *I* and *II* were measured with a Varian XL-100 apparatus at 31°C at 100 MHz, the ^{13}C NMR spectra of the compounds *I* were measured with a JEOL FX-100 apparatus and those of the compounds *II* with a Tesla BS 567 apparatus at 25°C at 25.1 MHz. The obtained ^1H NMR chemical shifts of the compounds *I* and *II* are given in Table I, the ^{13}C NMR shifts of the compounds *I* and *II* are given in Tables II and III, respectively.

RESULTS AND DISCUSSION

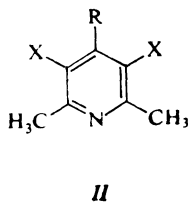
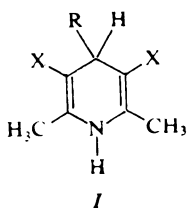
The chemical shifts of the protons and carbon atoms in the NMR spectra of the compounds *I* and *II* show the expected values^{16,17} (Tables I–III). The shifts of the protons bound at 4 position of the dihydropyridine nucleus of the compounds *I* form three separated groups according to character of the substituent R. The unusually high values of the chemical shift of the 4-proton (*i.e.* the proton attached to an sp^3 carbon atom) in the compounds *Ij–In* can be explained by the effect of the *o*-nitro group which is very close to this hydrogen atom both in crystalline state¹⁸ and, probably, in solution¹. A similar though less distinct differentiation of the chemical shift values can also be observed in the case of the N—H group signals. Comparison of spectra of the compounds in the series *I* and *II* shows that the chemical shifts of the comparable protons usually have higher values in the pyridine derivatives *II* than in the 1,4-dihydropyridine derivatives *I*. The signals of carbon atoms in the spectra of 1,4-dihydropyridine derivatives *I* were assigned with the help of the substituent effects¹⁹, off-resonance decoupling, and comparison within the whole series of the compounds *I*. This assignment agrees well with the values published² for a series of diesters of the type *I*. The signals of carbon atoms in the dihydropyridine

TABLE I

¹H NMR chemical shifts of the compounds *I* and *II* measured in hexadeuteriodimethyl sulphoxide with tetramethylsilane as the internal standard, the δ values in ppm (± 0.01)

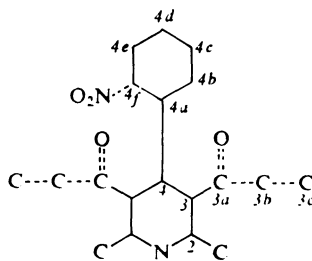
Compound	1,4-Dihydropyridines <i>I</i>					Pyridines <i>II</i>		
	CH ₃	C(4)—H	Ar—H	N—H	X	CH ₃	R	X
<i>a</i>	1.86	3.12	—	8.27	—	2.60	8.72	—
<i>b</i>	2.02	3.22	—	8.40	2.06	2.61	8.49	2.66
<i>c</i>	2.05	3.06	—	8.25	3.51	2.72	8.51	3.85
<i>d</i>	2.04	3.04	—	8.16	1.12	2.73	8.48	1.35
					3.97			4.33
<i>e</i>	1.98	4.31	7.16—7.38	8.52	—	2.78	7.60	—
<i>f</i>	2.13	4.98	7.11	8.78	2.21	1.93	7.06—7.51	2.40
<i>g</i>	2.19	4.81	7.08	8.68	3.47	2.50	7.06—7.53	3.50
<i>h</i>	2.20	4.78	7.08	8.63	1.06	2.51	7.05—7.52	1.86
					3.40			3.99
<i>j</i>	1.98	5.01	7.40—7.92	9.50	—	2.76	7.60—8.48	—
<i>k</i>	2.11	5.51	7.12—7.75	9.88	2.17	2.07	7.29—8.26	2.45
<i>m</i>	2.18	5.50	7.19—7.73	9.75	3.49	2.58	7.23—8.34	3.48
<i>n</i>	2.17	5.51	7.15—7.64	9.73	0.99	2.58	7.24—8.38	1.82
					3.80			3.93

nucleus were found in the range $\delta = 143.5\text{--}148.1$ ppm for the $\text{C}_{(2)}$ atom, in the range $\delta = 71.1\text{--}112.4$ ppm for the $\text{C}_{(3)}$ atom, and in the range $\delta = 24.5\text{--}41.3$ ppm for the $\text{C}_{(4)}$ atom. The values of chemical shifts of the $\text{C}_{(4)}$ atom show a distinct separation into three groups according to character of the substituent R (*Ia*–*Id*, *Ie*–*Ih*, *Ij*–*In*). The values of chemical shifts of the $\text{C}_{(3)}$ atoms show a distinct



	X	R		X	R
<i>a</i>	CN	H	<i>g</i>	COOCH ₃	C ₆ H ₅
<i>b</i>	COCH ₃	H	<i>h</i>	COOC ₂ H ₅	C ₆ H ₅
<i>c</i>	COOCH ₃	H	<i>j</i>	CN	<i>o</i> -O ₂ NC ₆ H ₄
<i>d</i>	COOC ₂ H ₅	H	<i>k</i>	COCH ₃	<i>o</i> -O ₂ NC ₆ H ₄
<i>e</i>	CN	C ₆ H ₅	<i>m</i>	COOCH ₃	<i>o</i> -O ₂ NC ₆ H ₄
<i>f</i>	COCH ₃	C ₆ H ₅	<i>n</i>	COOC ₂ H ₅	<i>o</i> -O ₂ NC ₆ H ₄

separation into four groups according to character of the substituent X, the values of chemical shifts increasing in the order of decreasing values of the σ constants of the respective substituents X. The signals of aromatic carbon atoms in the R substituents of the compounds *Ie*–*In* were assigned with the help of calculations based on the published¹⁹ increments supposing that the effect of the dihydropyridine nucleus attached by its 4 position is similar to that of isopropyl group. This method does not exclude possible confusion in the assignment of the values of chemical shift of $\text{C}_{(4b)}$ and $\text{C}_{(4c)}$ atoms in the aromatic ring. The signals in the ^{13}C NMR spectra of the pyridine derivatives *II* were assigned in similar way as those of the 1,4-dihydropyridines *I*, using, in addition, the modified ATP (Attached Proton Test) technique²⁰. The values of ^{13}C NMR chemical shifts of carbon atoms $\text{C}_{(2)}$, $\text{C}_{(3)}$, and $\text{C}_{(4)}$ of the pyridine ring were found in the δ ranges 152.4–164.3, 106.6–134.3, and 138.0–156.2 ppm, respectively. All the three cases mentioned show distinct separation of the values of chemical shifts into four groups according to character of the substituent X, the chemical shift values of $\text{C}_{(2)}$ and $\text{C}_{(4)}$ atoms being increased and those of $\text{C}_{(3)}$ being decreased with increasing values of σ constants of the substituents X. The assignment of signals to carbon atoms in the substituents R (*Iie*–*IIn*) was carried out in analogous way as in the series *I*. Comparison of the chemical shifts in the ^{13}C NMR spectra of the compounds *I* and *II* indicates that the signals



III

TABLE II
 ^{13}C NMR chemical shifts of the 1,4-dihydropyridines *I*. Measured in hexadeuteriodimethyl sulphoxide with tetramethylsilane as the internal standard, the δ values in ppm (± 0.05)

I^a	2	3	4	2a	3a	3b
<i>a</i>	148.1	77.1	24.9	17.3	119.0	—
<i>b</i>	144.8	107.5	26.2	18.3	196.4	29.6
<i>c</i>	146.3	96.8	24.5	17.4	167.2	50.2
<i>d</i> ^b	146.0	97.0	24.5	17.6	166.9	58.2
<i>e</i>	146.4	82.8	41.3	17.4	118.7	—
<i>f</i>	143.8	112.4	38.8	18.6	196.2	29.6
<i>g</i>	145.3	101.6	38.8	17.9	167.2	50.2
<i>h</i> ^c	144.8	101.9	38.8	17.9	166.8	58.6
<i>j</i>	147.9	81.6	36.5	17.8	118.7	—
<i>k</i>	143.5	112.3	34.5	18.5	196.5	29.9
<i>m</i>	145.9	101.3	34.1	17.8	166.7	50.2
<i>n</i> ^d	145.5	101.5	34.2	17.8	166.3	58.8

I^a	4a	4b	4c	4d	4e	4f
<i>e</i>	143.7	128.5	127.4	127.4	—	—
<i>f</i>	146.9	126.8	127.8	125.7	—	—
<i>g</i>	147.7	126.8	127.7	125.6	—	—
<i>h</i>	147.9	127.1	127.5	125.5	—	—
<i>j</i>	137.4	132.1	134.2	129.2	124.1	148.1
<i>k</i>	140.4	130.2	132.6	127.0	123.3	147.6
<i>m</i>	141.8	130.4	132.7	127.0	123.2	147.3
<i>n</i>	142.1	130.6	132.6	126.9	123.2	147.1

^a For the numbers of the individual centres see formula III; ^b 3c 14.1; ^c 3c 13.9; ^d 3c 13.6.

of the carbon atoms which form a part of the heterocyclic ring are higher in the pyridine derivatives *II* than in the dihydropyridines *I*. Using the least squares calculation, we tried to find a correlation between the chemical shifts of the C₍₂₎ atoms and we obtained the following regression line:

$$\delta(II) = 2.884 \pm 0.469\delta(I) - 261.577 \pm 2.193 \quad (\text{in ppm})$$

with the value of correlation coefficient $r = 0.88924$ which corresponds to a level of statistical significance of correlation better than 0.1%. For the chemical shifts

TABLE III

¹³C NMR chemical shifts of the pyridine derivatives *II*. Measured in hexadeuteriodimethyl sulphoxide with tetramethylsilane as the internal standard, the δ values in ppm (± 0.05)

<i>II</i> ^a	2	3	4	2a	3a	3b
<i>a</i>	164.3	106.6	144.8	23.8	115.6	—
<i>b</i>	158.7	130.3	138.0	24.2	200.0	29.4
<i>c</i>	161.5	122.6	140.1	24.3	165.7	52.3
<i>d</i> ^b	161.4	122.9	140.0	24.5	165.4	61.3
<i>e</i>	164.5	107.0	156.2	24.2	115.3	—
<i>f</i>	152.4	134.3	142.1	22.2	204.3	31.6
<i>g</i>	155.1	126.6	145.6	22.5	167.7	52.1
<i>h</i> ^c	154.9	126.8	145.6	22.5	167.2	61.1
<i>j</i>	164.5	106.7	154.6	24.1	114.5	—
<i>k</i>	152.6	133.0	139.6	22.5	203.6	31.3
<i>m</i>	156.3	124.8	144.9	23.3	166.8	52.1
<i>n</i> ^d	156.2	125.0	144.6	23.1	166.2	61.2

<i>II</i> ^a	4a	4b	4c	4d	4e	4f
<i>e</i>	133.6	128.9	130.7	128.7	—	—
<i>f</i>	135.4	129.1	129.2	128.7	—	—
<i>g</i>	136.1	128.3	128.7	127.8	—	—
<i>h</i>	136.2	128.1	128.6	126.8	—	—
<i>j</i>	128.6	132.6	135.3	131.7	125.6	146.6
<i>k</i>	129.7	132.3	133.0	131.0	125.1	147.8
<i>m</i>	131.2	130.9	133.7	130.4	124.5	147.2
<i>n</i>	131.5	131.3	133.8	130.4	124.5	147.3

^a For the numbers of the individual centres see formula *III*; ^b 3c 14.1; ^c 3c 13.4; ^d 3c 13.3.

of $C_{(3)}$ we calculated the regression line:

$$\delta(II) = 0.8497 \pm 0.038\delta(I) + 39.105 \pm 1.475 \quad (\text{in ppm, Fig. 1}).$$

The correlation coefficient $r = 0.9901$ shows that the effects affecting the value of chemical shift of $C_{(3)}$ atoms are, in the compound series *I* and *II*, analogous in the dependence on the character of the X and R substituents. For the chemical shifts of $C_{(4)}$ atoms the following regression straight line was calculated:

$$\delta(II) = 0.5454 \pm 0.2233\delta(I) + 126.626 \pm 4.701 \quad (\text{in ppm, Fig. 2}).$$

Low value of the correlation coefficient $r = 0.6113$ (the statistical significance level of 2%) and high standard deviations indicate that in this case, obviously, besides different hybridisation at the $C_{(4)}$ atom, also different sterical requirements of the R substituent is significant, which affects conformation of the 1,4-dihydropyridine ring in solution¹. We also tried to find the dependence of the ^1H shift of the hydrogen at $C_{(4)}$ on the ^{13}C shift of the $C_{(4)}$ atom in the 1,4-dihydropyridines (*I*). The following regression straight line was calculated:

$$\delta(^1\text{H}) = 0.1241 \pm 0.0301\delta(^{13}\text{C}) + 0.1910 \pm 0.0637 \quad (\text{in ppm}).$$

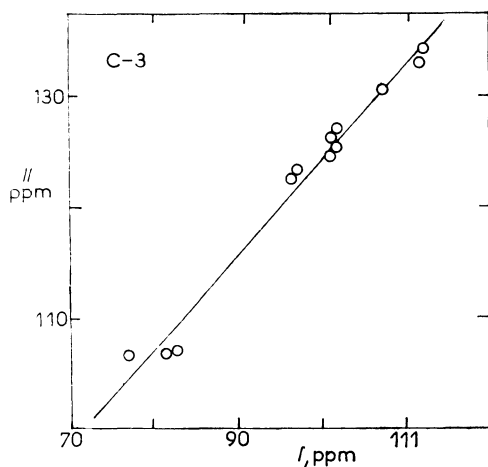


FIG. 1

Mutual dependence between the ^{13}C NMR chemical shifts of the $C_{(3)}$ atoms of the compound series *I* and *II*

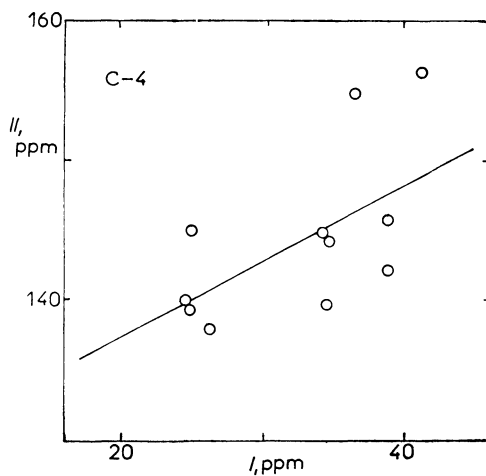


FIG. 2

Mutual dependence between the ^{13}C NMR chemical shifts of the $C_{(4)}$ atoms in the compound series *I* and *II*

The correlation coefficient $r = 0.8087$ (the statistical significance level is better than 1%) indicates that the sterical effect of the substituent R has a somewhat different effect on the environment of the $\text{C}_{(4)}\text{—H}$ hydrogen atom than on that of $\text{C}_{(4)}$ atom. This result is probably due to greater proximity¹ of the hydrogen to the nitro group in compounds *Ik–In*. We also tried to find a relation (linear regression, factor analysis) between the ^{13}C chemical shifts of carbon atoms in the dihydropyridine nucleus of compounds *I* and the wavelengths of the longest-wave and the shortest-wave absorption maxima in their electronic spectra²¹. However, no correlation was found in this case. Similarly, the attempts to find a correlation between the ^{13}C chemical shifts of the $\text{C}_{(4)}$ atoms in compounds *I* and their oxidation potentials²² (E_p) failed, too.

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Translated by J. Panchartek.