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THE N.M.R. AND MASS SPECTROSCOPIC STUDIES OF 3-ACETYL-5-ALKYL-1-BENZYL-1,4-DIHYDROPYRIDINES.

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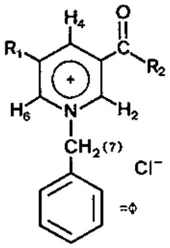
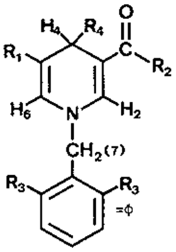
Abstract : A novel series of 3-acetyl-5-alkyl-1-benzyl-1,4-dihydropyridines (alkyl : methyl ; ethyl ; isopropyl ; n-propyl) is synthesised. ^{1}H-NMR-spectra are discussed. A mass spectral fragmentation is elaborated using high resolution mass measurements, metastable defocusing technique and deuterium labelling.

Because of the increasing interest in 1,4-dihydropyridine compounds as possible models for NAD(H) (1-3) and their application as potential drugs (4-8) a series of 3-acetyl-5-alkyl-1-benzyl-1,4-dihydropyridines has been synthesised. Dihydropyridine compounds of the Hantzsch-ester type have already been thoroughly investigated in this laboratory. Spectral data were published (9,10) as well as kinetic study of the behaviour towards the reduction of activated ketones such as chloranil.(11) In this paper ^{1}H-NMR and mass spectral data of 3-acetyl-5-alkyl-1-benzyl-1,4-dihydropyridines are reported, as well as the ^{1}H-NMR data of their precursors the corresponding pyridinium salts. The 3-acetyl-5-alkyl-1-benzylpyridinium chlorides (I to IV) were obtained by condensation of the 3-acetyl-5-alkylpyridines (12) with benzyl chloride in dry methanol.(13) The 1,4-dihydropyridines (V to VIII) were obtained by the action of sodium dithionite on the corresponding salts. (13,14)





I $R_1 = \underset{a}{CH_3}$-; $R_2 = \underset{d}{CH_3}$-

II $R_1 = \underset{b}{CH_3}—\underset{a}{CH_2}$-; $R_2 = \underset{d}{CH_3}$-

III $R_1 = (\underset{b}{CH_3})_2\underset{a}{CH}$-; $R_2 = \underset{d}{CH_3}$-

IV $R_1 = \underset{c}{CH_3}—\underset{b}{CH_2}—\underset{a}{CH_2}$-; $R_2 = \underset{d}{CH_3}$-

V $R_1 = \underset{a}{CH_3}$-; $R_2 = \underset{d}{CH_3}$-; R_3= H-; R_4= H-

VI $R_1 = \underset{b}{CH_3}—\underset{a}{CH_2}$-; $R_2 = \underset{d}{CH_3}$-; R_3= H-; R_4= H-

VII $R_1 = (\underset{b}{CH_3})_2\underset{a}{CH}$-; $R_2 = \underset{d}{CH_3}$-; R_3= H-; R_4= H-

VIII $R_1 = \underset{c}{CH_3}—\underset{d}{CH_2}—\underset{a}{CH_2}$-; $R_2 = \underset{d}{CH_3}$-; R_3= H-; R_4= H-

IX $R_1 = CH_3$-; $R_2 = CH_3$-; R_3= Cl; R_4= D-

X $R_1 = CH_3$-; $R_2 = CD_3$-; R_3= H-; R_4= H-

Compounds IX and X were synthesised for mass spectral purposes. As to compound IX, it can be obtained from the corresponding salt, but performing the sodium dithionite reduction in D_2O instead of H_2O. Compound X is formed by the action of C_2H_5ONa on compound V in C_2H_5OD. The structure of compounds IX and X was confirmed by ^{1}H-NMR spectroscopy.

100 MHz ^{1}H-NMR data of 3-acetyl-5-alkyl-1-benzylpyridinium salts. (I to IV)

The 100 MHz ^{1}H-NMR data of the pyridinium salts (I to IV) are summarised in table 1. The positions of the aromatic ring protons H_2, H_4 and H_6 compared to the δ-values of the same protons in the free pyridine bases (12) are all shifted downfield.(table 2) This can be understood as the result of a lowered π-electron density in the heterocyclic aromatic system due to quaternisation of the ring nitrogen.(15)

Table 1

100 MHz ^{1}H-NMR data of 3-acetyl-5-alkyl-1-benzylpyridiniumchlorides[a] (I to IV). Chemical Shift values (δ) in D_2O, internal reference TSP[a].

	a	b	c	d	H_2	H_4	H_6	H_7	Φ
I	2.68	-	-	2.84	9.35	8.92	9.02	5.92	7.56
II	3.04	1.44	-	2.88	9.44	9.04	9.16	6.00	7.60
III	3.45	1.52	-	2.88	9.44	9.04	9.16	6.04	7.60
IV	2.74	1.76	1.16	2.88	9.52	8.92	9.28	6.08	7.60

Coupling constants: For the coupling constants J_{ab} and J_{bc} a value of 8 Hz is found in all the spectra. The meta coupling constants J_{H2H4} and J_{H4H6} *approximate 2 Hz. The coupling constant* J_{H2H6}= 0 Hz.

Table 2

Difference between the chemical shift values (Δδ) of the aromatic H_2, H_4 and H_6 pyridine ring protons in the free 3-acetyl-5-alkylpyridines and their N-benzyl derivatives.[b]

	H_2	H_2s	ΔH_2	H_4	H_4s	ΔH_4	H_6	H_6s	ΔH_6
I	8.92	9.35	0.43	8.0	8.92	0.92	8.60	9.02	0.42
II	8.80	9.44	0.64	7.86	9.04	1.18	8.44	9.16	0.72
III	9.00	9.44	0.44	8.08	9.04	0.96	8.68	9.16	0.48
IV	8.92	9.52	0.60	8.0	8.92	0.92	8.52	9.28	0.76

[a] TSP : 3-(trimethylsilyl)propanesulfonic acid sodium salt.

[b] Chemical shift values are uncorrected for solvent effects.
H_i: Chemical shift in the 3-acetyl-5-alkylpyridines.
H_is : " " " " *corresponding salts.*

100 MHz ^{1}H-NMR data of 3-acetyl-5-alkyl-1-benzyl-1,4-dihydropyridines. (V to VIII)

The 100 MHz ^{1}H-NMR spectra of compounds V to VIII are summarised in table 3. They were recorded in $(CD_3)_2CO$. Although these products were soluble in $CDCl_3$, this solvent was not used in order to avoid possible reactions. Indeed, 1,4-dihydropyridine compounds of the Hantzsch-ester type suffered a fast aromatisation reaction in this solvent.(11) However, recent experiments have shown that our products are stable in a $CDCl_3$ solution. The resonance signals of the ring substituents appear at δ-values normally to be expected on a diene system.

Table 3

100 MHz ^{1}H-NMR data of 3-acetyl-5-alkyl-1-benzyl-1,4-dihydropyridines. (V to VIII) Chemical shift values (δ) in $(CD_3)_2CO$, internal reference TMS.

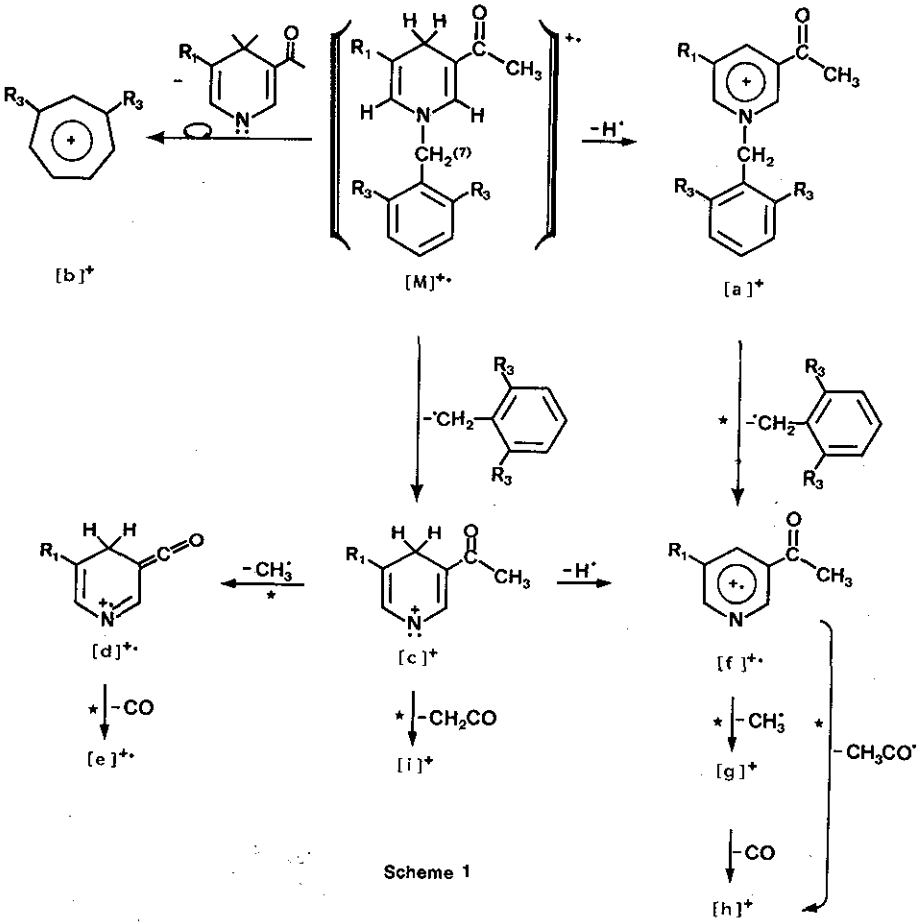
	a	b	c	d	H_2	H_4	H_6	H_7	Φ
V	1.52	-	-	2.08	7.48	2.84	5.76	4.52	7.32
VI	1.88	0.96	-	2.08	7.48	2.92	5.76	4.50	7.34
VII	2.04	0.92	-	2.08	7.33	2.92	5.72	4.48	7.25
VIII	1.84	1.32	0.80	2.04	7.36	2.86	5.72	4.44	7.28

Coupling constants: For the vicinal coupling constants J_{ab} and J_{bc} 8 Hz is found in all the spectra. For the allylic coupling constants J_{H2H4}, J_{H4H6} and J_{H6Ha} = 2 Hz is observed.

The H_2-proton resonates at an average value of 7.41 δ next to the aromatic signal of the N-benzyl group. The H_4- and H_6-protons appear at mean δ-values of 2.88 and 5.74 respectively. These signals are broadened by an existing allylic coupling of 2 Hz between H_2-H_4 and H_4-H_6. The extra broadening of the H_6-signal is caused by an additional allylic coupling with the protons on the 5-alkyl substituent. These results are obtained by double resonance experiments.

Mass spectral data of 3-acetyl-5-alkyl-1-benzyl-1,4-dihydropyridines. (V to VIII)

Mass spectral data on 1,4-dihydropyridine compounds are rather scarce. (10, 16-18) Typical ions in the fragmentation pattern of compounds V to VIII are presented in table 4. They are of potential diagnostic use in problems involving structure eludication of minor quantities of these compounds. The fragmentation pattern under electron impact of 3-acetyl-5-alkyl-1-benzyl-1,4-dihydropyridines is rather straightforward.(Scheme 1)



Scheme 1

A significant mode of decomposition of the molecular ion $[M]^{+\cdot}$ is the cleavage of the N-C_7 bond. This cleavage results in either ion $[b]^+$ or in the 1,4-dihydropyridine moiety $[c]^+$, both intense peaks in the mass spectrum. These ions give information on the nature of the N-substituent and the heterocyclic part of the molecule. The base peak in the N-benzyl derivatives is found at an m/e-value of 91.(ion $[b]^{+}$) This observation is however not a rule of thumb. Indeed, Lyle et al. (18) who examined a series of 2-aryl-1-benzyl-1,2-dihydropyridines observed a base peak resulting from the loss of the 2-aryl function out of the molecular ion $[M]^{+\cdot}$. This is not surprising since by this process aromatisation of the molecular ion can occur by the loss of a stable aryl radical. This aromatisation process also occurs in our products although less, since a H$^{\cdot}$radical has to be expelled. This H$^{\cdot}$-radical originates from the C_4-position as could be observed in the mass spectrum of the deuterated compound IX, were both $[M - H]^{+}$- and $[M - D]^{+}$-ions were detected.

Table 4

Low resolution mass spectra of 3-acetyl-5-alkyl-1,4-dihydropyridines (V to VIII) and deuterated analogues (IX to X).[c]

	V	VI	VII	VIII	IX	X
$[M]^{+\cdot}$	227[40]	241[35]	255[38]	255[32]	296[19][d]	230[22]
$[a]^{+}$	226[10]	240[11]	254[15]	254[10]	295[8] -H$^{\cdot}$ 294[3] -D$^{\cdot}$	229[11]
$[b]^{+}$	91[100]	91[100]	91[100]	91[100]	159[85][d]	91[100]
$[c]^{+}$	136[55]	150[59]	164[52]	164[53]	137[100]	139[47]
$[d]^{+}$	121[2<]	135[3]	149[2]	149[3]	122[2]	121[2]
$[e]^{+}$	93[3]	107[2<]	121[<2]	121[<2]	94[5]	93[6]
$[f]^{+}$	135[5]	149[7]	163[5]	163[4]	136[9]	138[17]
$[g]^{+}$	120[7]	134[8]	148[16]	148[11]	121[7]	120[7]
$[h]^{+}$	92[22]	106[5]	120[6]	120[6]	93[10]	92[25]
$[i]^{+}$	94[10]	108[13]	122[16]	122[10]	95[17]	95[19]

[c] Relative intensities are given in parenthesis.

[d] ion peaks for Cl^{35}.

In this deuterated N-2,6-dichlorobenzyl derivative IX, the base peak in the mass spectrum is due to ion $[c]^+$, the 2,6-dichlorobenzyl part is revealed by ions at m/e-values 159, 161 and 163 together with ions at m/e 126 and 124 by subsequent loss of a $Cl^{\cdot}$-radical out of the former ions.

Most of the ions encountered in the mass spectra of 3-acetyl-5-alkyl-1,4-dihydropyridines originate from ion $[c]^+$. Loss of 15 a.m.u. by the loss of a $CH_3^{\cdot}$-radical (ion $[d]^+$) followed by the expulsion of a neutral molecule of CO (ion $[e]^+$) was observed. Metastable ions were observed by the "metastable defocusing" technique (19) (H.V-scan) indicating that ion $[h]^+$ also was formed in a one step procedure by the loss of a $CH_3CO^{\cdot}$-radical. Ion $[c]^+$ also gave rise to ion $[i]^+$ by the expulsion of a molecule of ketene. This rearrangment process was confirmed by deuterium labelling. Indeed, loss of 44 a.m.u. was observed out of structure $[c]^+$ in the mass spectrum of 3-acetyl-d_3-5-methyl-1-benzyl-1,4-dihydropyridine (X). The elemental composition of the ions was confirmed by high resolution mass measurements. Mass spectra were recorded on a Jeol 01-SG-2-special mass spectrometer. The samples were vapourised by means of a direct insertion probe. The ionising voltage was maintained at 70 eV and the source temperature at 200°C.

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