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PROTON AND CARBON NUCLEAR MAGNETIC RESONANCE STUDY ON SOME N- AND O-ACYL DERIVATIVES OF MONOHYDROXYPYRIDINES. (§)

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Abstract- A comparative study on the proton and carbon NMR spectra for a series of N- and O-acyl substituted monohydroxypyridines (C_5H_4NOR: R -H, -CHO, $-COCH_3$, $-COC(CH_3)_3$, $-COCF_3$, $-COC_6H_5$, $-SO_2CH_3$, $-SO_2C_6H_4CH_3$ p) is reported.

Characteristic ^1H, ^{13}C NMR and IR spectral features allow simple and unambiguous distinction between the isomeric N- and/or O-acyl-derivatives of 2-, 3- and 4-hydroxypyridines, so that both forms can clearly be identified when tautomeric equilibria occur, since the tautomerism rate is slow on the NMR time scale.

Although in the last few years some isomeric acyl derivatives of 2 and 4 hydroxypyridines (2 and 4 pyridones), have been submitted to ^1H [1-4,9], ^{13}C [5-11] and ^{14}N [12] NMR studies and several N- and O acyl derivatives of 4 hydroxypyridine have been prepared [13-15], apparently a general and comprehensive study on N- and O-acyl derivatives of the three isomeric monohydroxypyridines has not been undertaken. In particular, little work has been done in the ^{13}C NMR area, although this technique is invaluable in providing structural information on organic molecules.

A ^{13}C and ^1H NMR study supported by IR data aimed at elucidating the influence of the introduced acyl substituent on the structure of the resulting derivatives of 2,3- and 4-hydroxypyridines was therefore undertaken.

Thus, the acyl substituents -COR and $-SO_2R$, with R representing either an electron-releasing or an electron-withdrawing group, were examined and the following compounds were prepared and studied: formyl, acetyl, pivaloyl, trifluoroacetyl, benzoyl, methanesulfonyl and p-toluenesulfonyl derivatives (see Scheme 1). The study was also extended to the 1-(2'-pyridyl)-2 pyridone (6) [16] and 1-(4'-pyridyl)-4 pyridone (7) [17], both having an electron-attracting group, the pyridine moiety, bound to the pyridone nitrogen atom. The new compounds 3- and 4 acetoxy-N-methylpyridinium iodides (9 and 10) were also studied in order to obtain information on the effect of charge in comparison with the uncharged acetoxy derivatives.

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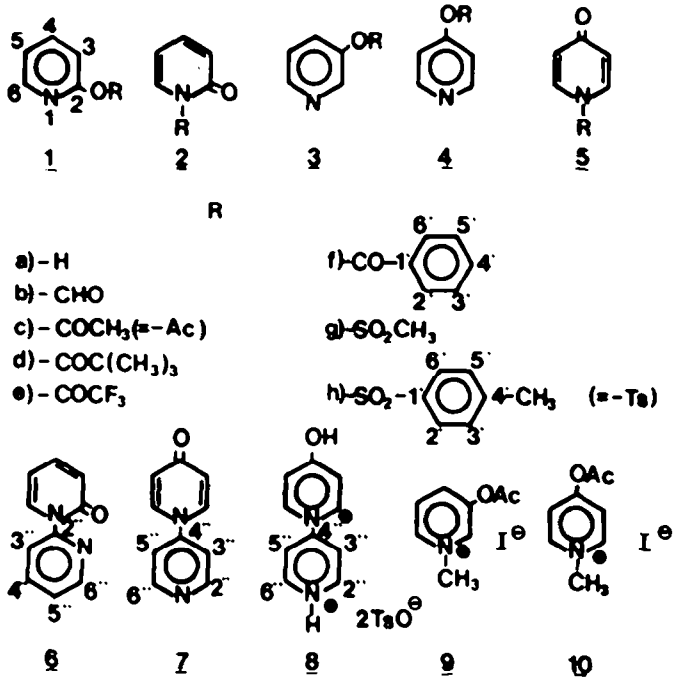
^{13}C AND ^{1}H NMR SPECTRA

The ^{13}C and ^{1}H NMR chemical shifts of 2-, 3 and 4-hydroxypyridine (2- and 4-pyridone) moieties are reported in Tables 1 and 2 respectively.



SCHEME 1

The ^{13}C assignment were obtained on the basis of off-resonance spectra, proton coupled spectra, ^{1}H selective decoupling experiments, comparison with model compounds, empirical rules [18] and internal consistency. The ^{1}H NMR analysis was carried out according to the chemical shift and J coupling constant values of the ring protons. The J values were been obtained from computer analysis of the ^{1}H-NMR spectra at 90 MHz. The final parameters resulted from iterative computer simulation of experimental spectra using the ITRCAL program on a BNC-28 Bruker computer.

O-Substituted-2-hydroxypyridines (1) and N-substituted-2-pyridones (2 and 6) (Tables 1A and 2A)

Although in the ^{13}C NMR spectra atoms C-4 and C-6 show very similar shifts, they could be unambiguously distinguished by different coupling constants with their attached protons [19,20]. Moreover, C-3 and C-5 exhibit different multiplicities (due to different ^{1}H long-range coupling constants) in the proton-coupled spectra [21,25]; C-2 assignement is easy on the basis of off-resonance experiments. Ambiguities in C-2 assignment due to the presence of other quaternary carbon atoms carrying substituents are resolved by comparison with the spectra of their 3- and 4- analogues.

As already observed, the 2-derivatives (collected in Scheme 1) may exist in the isomeric forms 1 and 2. 2-hydroxypyridine is known to exist [12] in the pyridone form (2a) while other derivatives seem to exist in the pyridone form (1) [15].

Such a structural difference involves some characteristic modifications of the spectral features of form 1 in comparison with 2: in form 1 C-3 exhibits an upfield shift, C-5 a downfield shift so that a C-3, C-5 chemical shift inversion occurs between the two forms; also the C-6 resonance is very sensitive to structure isomerism and shows in form 1 a downfield shift of more than 12 ppm; quaternary C-2 carbons atoms are shifted 6-9 ppm upfield in form 1. On the other hand, C-4 atoms seem less sensitive to tautomeric isomerism and show only a 1 ppm difference in the two forms.

Thus, it is possible to attribute structure 1 ($CDCl_3$ solutions) either to the new compounds here described (R= d, e, g)or to known molecules which appear hitherto not to have been submitted to NMR study (R= f, h), by comparing their data with those of derivatives of established structure

Table 1. ^{13}C NMR chemical shifts of the pyridine or pyridone moiety in ppm from TMS ($CDCl_3$ solution) at 22.63 MHz.

A) Compounds 1, 2, 6

	1c	1d	1e	1f	1g	1h	2a	2b	2c	6	N-methyl-2-pyridone (5)
C-2	157.44	158.11	155.68	157.88	157.44	156.94	165.40	162.75	162.30	162.08	161.8
C-3	116.35	116.57	115.24	116.35	115.68	115.91	120.33	123.64	123.64	121.43	119.1
C-4	139.33	139.33	140.43	139.33	140.65	140.21	141.54	141.98	140.43	140.21	139.5
C-5	121.87	121.65	123.64	121.87	122.76	122.76	106.85	107.29	106.63	106.63	104.8
C-6	148.16	148.16	148.61	147.94	147.94	148.16	134.35	127.62	130.49	136.01	139.5

B) Compounds 3, 9

	3a	3c	3d	3e	3f	3g	3h	9*	N-methyl-3-pyridone § (5)	N-phenyl-3-pyridone § (11)
C-2	136.90	143.30	142.86	142.42	142.86	143.52	143.96	140.94	134.4	134.9
C-3	155.23	147.06	147.72	146.18	147.72	145.91	146.62	150.22	168.8	168.4
C-4	125.19	128.94	128.94	128.72	129.83	129.61	128.00	140.05	131.7	132.8
C-5	125.19	123.64	123.64	124.74	124.08	124.30	124.08	129.67	126.3	127.5
C-6	139.55	146.62	146.17	148.16	145.18	148.16	147.94	146.34	121.4	125.7

C) Compounds 4, 5, 7, 8, 10

	4c	4d	4e	4f	4g	4h	5a	5c	5g	5h	7	8§	10*	N-methyl-4-pyridone § (5)
C-2, C-6	151.48	150.24	151.92	151.04	151.70	151.92	136.88	134.24	134.46	134.68	137.56	147.70	150.33	141.4
C-3, C-5	117.01	116.79	115.46	117.45	116.57	117.23	117.23	118.78	119.44	119.66	119.88	116.33	121.49	117.2
C-4	159.77	157.66	155.90	158.11	156.12	156.78	178.21	180.64	177.32	181.75	181.53	174.66	164.35	176.6

*CD_3CN solution
§$DMSO\text{-}d_6$ solution

(R= a, c).

A tautomeric equilibrium was observed only for 1c and 2c [1], while the b derivative exists only in the pyridone form (2) [14] as compound 6, the pyridone structure of which is well known [3]. These results have been confirmed by ^{1}H NMR spectra.

An ABCD spectrum is shown by four protons of the heteroaromatic ring. Comparison of the chemical shift values of compounds 1, 2 and 6 (Table 2A) shows large and constant differences. In compounds 2 and 6 ring protons are shifted upfield as compared to the corresponding protons of 1: H-3, $\Delta\delta$ 0.45-0.65 ppm; H-4, $\Delta\delta$ 0.40-0.50 ppm; H-5, $\Delta\delta$ 0.9-1.0 ppm; H-6, $\Delta\delta$ 0.40-0.50 ppm. Such an effect may be ascribed to differences of ring current between the pyridone and the pyridine ring systems.

Information on the structure of O-substituted hydroxypyridines and N-substituted pyridones can be also obtained from coupling constant values of the ring protons. Such an analysis was applied to derivatives 1c, e and 2b c in order to obtain J values typical for structure 1 and 2. Some J values, compared with those already published for similar compounds, are reported in Table 3. Figures for the most significant vicinal couplings $J_{3,4}$, $J_{4,5}$ and $J_{5,6}$ indicate remarkable differences between pyridone and pyridinol derivatives. In particular, $J_{3,4}$ and $J_{5,6}$ values are always much higher in pyridone structures while $J_{4,5}$ are lower. Such an effect appears to be general and not restricted only to the N- and O-acyl derivatives under study, as seen in the reported J values in N-methyl-2-pyridone and 2-methoxypyridine [5]. A further support for the structure 2b is given by additional splitting observed in H-3 and H-5 resonances due to long-range coupling with the formyl proton; such a five bonds coupling (0.6 Hz) can occur to H-3 and H-5 only when the formyl group is on the nitrogen atom [26 b]

O-Substituted-4-Hydroxypyridines (4, 8 and 10) and N-substituted-4-pyridones (5 and 7) (Tables 1C and 2C).

Owing to the symmetry of these derivatives, their ^{13}C spectra are particulary simple. Only three peaks are present, at about 115-120 ppm (C-3, C-5), 134-152 ppm (C-2, C-6) and 155-182 ppm (C-4).

It has been shown that 4-hydroxypyridine must be formulated as 4-pyridone 5a [5, 12]; our data ($CDCl_3$ solution) agree, and indicate unambiguously the structure of all compounds herein studied.

In fact, unequivocal information on tautomeric forms can be obtained from the chemical shifts of the quaternary C-4 and the methyne C-2 and C-6 atoms. In the pyridone structures 5, while C-4 shows a large downfield shift (20-25 ppm), C-2 and C-6 are shifted unfield (10-15 ppm) in comparison with the corresponding atoms of structures 4. C-3 and C-5 are less sensitive to structures modifications, and show small shifts (less than 2 ppm upfield in forms 4).

Therefore, it was possible to deduce that substituents d, e and f give rise only to form 4, while substituent c generates in $CDCl_3$ solution the known tautomeric equilibrium of 4 and 5 [2] as for forms 1 and 2 [1]. Each resonance pattern can be unequivocally assigned to each pure tautomer 4 or 5, because the observed chemical shifts are identical to those shown by either isolated pure forms.

Substituents g and h gave rise to both isomeric structures having independent existence. They undergo no tautomeric equilibria since neither form generates the other in solution (4h, 5h) and the existence of each form in solution seems to be independent of the other (4g, 5g).

Table 2. ^{1}H NMR chemical shifts of the pyridine or pyridone moiety in ppm from TMS ($CDCl_3$ solution) at 90.1 MHz.

A) Compounds 1, 2, 6

	1c	1d	1e	1f	1g	1h	2a	2b	2c	6
H-3	7.07	7.00	7.25	ca.7.20	7.12	7.10	6.60	6.58	6.53	6.64
H-4	7.78	7.77	7.94	7.73	7.83	7.76	7.47	7.40	7.30	7.42
H-5	7.22	7.25	7.39	ca.7.20	7.27	7.24	6.30	6.27	6.17	6.31
H-6	8.40	8.38	8.40	8.33	8.33	8.24	7.43	7.83	7.94	7.89

B) Compounds 3, 9

	3a	3c	3d	3e	3f	3g	3h	9*
H-2	8.22	8.37	8.42	8.77	8.60	8.57	8.17	8.75
H-4	7.24	7.44	7.47	7.97	ca.7.50	7.70	7.50	8.33
H-5	7.20	7.27	7.27	7.70	ca.7.50	7.37	7.36	8.03
H-6	8.05	8.44	8.47	8.65	8.58	8.57	8.53	8.63

C) Compounds 4, 5, 7, 8, 10

	4c	4d	4e	4f	4g	4h	5a	5c	5g	5h	7	8§	10*
H-2, H-6	8.56	8.58	8.73	8.73	8.67	8.57	7.66	8.09	7.85	7.90	7.73	8.80	8.83
H-3, H-5	7.09	7.10	7.27	7.32	7.23	7.00	6.46	6.31	6.40	6.32	6.57	7.10	7.82

* CD_3CN solution
§ DMSO-d_6 solution

Table 3. Characteristic J_{H-H} coupling constants values (Hz) of pyridinic and pyridonic ring protons

	2-methoxy--pyridine (5)	1c	1e	2b	2c	6 (3)	N-methyl-2 -pyridone (5)
$J_{3,4}$	8.45	8.75	7.88	9.15	9.40	9.11	9.05
$J_{3,5}$	0.90	0.80	0.02	1.17	1.35	1.29	1.35
$J_{3,6}$	0.85	0.75	0.00	0.70	0.70	0.71	0.70
$J_{4,5}$	7.10	8.10	8.15	6.46	6.65	6.52	6.65
$J_{4,6}$	2.00	2.00	2.50	2.17	2.10	2.03	2.10
$J_{5,6}$	5.05	5.50	6.50	6.94	7.50	6.79	6.60

	3-methoxy--pyridine (5)	3c	3h	3-formyl--pyridine (26c)	3-acetyl--pyridine (26c)	3a	N-methyl-3 -pyridone (5)
$J_{2,4}$	3.00	2.40	2.50	2.02	2.12	2.80	2.70
$J_{2,5}$	0.70	0.80	0.80	0.88	0.83	0.70	0.20
$J_{2,6}$	-0.35	0.20	0.00	0.00	0.00	-0.15	1.70
$J_{4,5}$	8.65	8.00	8.50	7.85	7.99	8.35	9.00
$J_{4,6}$	1.40	1.70	1.55	1.81	1.79	1.45	1.00
$J_{5,6}$	4.75	4.80	5.05	5.00	4.87	4.65	5.50

	4-methoxy--pyridine (5)	4c	5c	7	N-methyl-4-pyridone (5)
$J_{2,3}$	5.75	6.00	8.20	7.50	7.55
$J_{2,5}$	0.60	0.75	0.20	0.10	0.15
$J_{2,6}$	-0.20	0.00	2.00	2.50	2.50
$J_{3,5}$	2.60	2.00	3.00	2.80	2.85
$J_{3,6}$	0.60	0.75	0.20	0.10	0.15
$J_{5,6}$	5.75	6.00	8.20	7.50	7.55

Moreover, the ^{13}C, and ^{1}H chemical shifts indicate a structural difference between 7 and its tosyl salt 8. In fact, while the chemical shifts of 7 show values attributable to a pyridone moiety, they indicate for 8 a hydroxypyridine structure. A significant effect on the chemical shifts of the latter compound due to the presence of a charge on the nitrogen atom may be excluded by comparing the δ values of compounds 4 and 10, 3 and 9.

The ^{1}H spectra show an AA'BB' system for the four protons of the heteroaromatic ring, with two apparent triplets for H-3 and H-5 at higher field, and for H-2 and H-6 at lower field. In compound 5 and 7 both resonance peaks are shifted upfield as compared to the corresponding resonances in compounds 4, 8, and 10: $\Delta\delta$=0.5-0.7 ppm for H-2 and H-6; $\Delta\delta$ 0.6-0.8 ppm for H 3 and H 5 (Table 2C). These $\Delta\delta$'s agree with the differences reported between pyridone and pyridinol structures [5].

The vicinal $J_{2,3}$ and $J_{5,6}$ are always greater in pyridones, and this can be used to discriminate between the two forms, as further supported also by comparing vicinal J values of N-alkyl 4--pyridones and 4-alkoxy-pyridines [5] (Table 3).

The structure may be more directly derived from the splitting of most intense multiplet bands, which however represents the sum $J_{2,3} + J_{2,5}$ ($J_{AB} + J_{AB'}$). Also in this case, this splitting is greater (8.2-8.4 Hz) in N-acyl or N-aroyl-4-pyridones than in O-acyloxy-4-pyridines (6.2 6.4 Hz).[13]

O-Substituted-3-hydropyridines 3 and 9 (Tables 1B and 2B).

These derivatives of 3-hydroxypyridine show a unique resonance pattern, and the peaks were assigned following the described general criteria [8]. The pyridone structure coul be excluded on the basis of different experiments [5,11,12], and the chemical shifts point out the aromatic pyridine structure.

The examined 3-O-acyl derivatives show differences in ^{13}C chemical shifts. These can be attributed to the different contributions induced by the various substituents and they do not indicate structural changes.

These conclusion are also confirmed by the ^{1}H-NMR spectra. In fact the ^{1}H ring protons chemical shift (Table 2B) are quite similar to these of typical aromatic systems [26] and the observed differences among the substituents can be ascribed to the different ring currents induced by the different substituents.

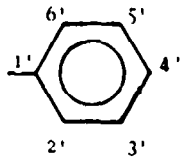
A higher degree of aromaticity can therefore be postulated for compounds 3, in comparison with their corresponding 2- and 4- analogues. This hypothesis is supported by a coupling constant analysis of the pyridine ring protons.

The four pyridine protons were considered as an ABMX system; in fact, calculation leads to J values (Table 3) very close to those reported for pyridine carrying in position 3 either an electrophilic or a nucleophilic substituent. This fact indicates a common structure for all 3-substituted pyridines and implicates, therefore, a 3-acyloxypyridine structure (3) for these derivatives.

Significant differences of ^{13}C chemical shift were found among compounds 3a, 3c-h and N-methyl [5] or N-phenyl-3-pyridones [11]: in 3-hydroxypyridine, C-2 and C-6 shows upfield shifts from the corresponding carbon atoms of the 3-O derivatives, C-4 and C-5 resonances coincide at 125-19 ppm. The observed $\Delta\delta$'s of C-3 appear to be of particular importance in the aforementioned compounds: compared with the chemical shift in 3-acyloxypyridines, C-3 of (3a) shows a downfield shift of about 8 ppm, while in N-methyl- and N-phenyl-3-pyridones it resonates about 21 ppm downfield. These C-3 chemical shift differences suggest for (3a) a somewhat different structure from

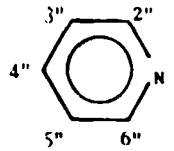
Table 4. ^{13}C NMR chemical shifts of carbon atoms of substituent groups in ppm from TMS ($CDCl_3$ solution) at 22.63 MHz.

2b	160.98	(C=O)			-										
1c	168.27	"	20.24	(CH_3)	-										
2c	162.30	"	26.64	"	-										
3c	168.49	"	20.24	"	-										
4c	167.17	"	20.90	"	-										
5c	167.39	"	21.33	"	-										
1d	173.35	"	26.20	"	40.12	$\underline{C}(CH_3)_3$									
3d	176.22	"	26.42	"	38.80	"									
4d	175.34	"	26.20	"	39.68	"									
1e	153.91	"	-		114.80	(CF_3)									
3e	154.77	"	-		114.58	"									
4e	152.58	"	-		114.13	"									



	1'	2',6'	3',5'	4'
1f	132.48	130.04	128.32	133.58
3f	132.38	130.49	128.72	133.77
4f	132.61	130.49	128.94	134.47
1h	133.80	128.72	129.83	145.29
3h	132.04	128.50	130.27	145.73
4h	132.26	128.50	130.05	146.18
5h	132.25	127.62	131.15	147.06

1g	-		40.59	(CH_3)	-										
3g	-		37.47	"	-										
4g	-		38.13	"	-										
5g	-		42.11	"	-										



	2"	3"	4"	5"	6"
6	151.92	122.09	137.56	123.20	148.83
7	152.14	115.91	149.05	115.91	152.14
8*	143.72	120.08	152.15	120.08	143.72

8§	168.78	(C=O)	21.18	"	49.69	(N^+-CH_3)									
10§	167.89	"	21.62	"	49.02	"									

* CD_3CN solution
§ DMSO-d_6 solution

Table 5. ^{1}H NMR chemical shifts of protons of substituent groups in ppm from TMS ($CDCl_3$ solution) at 90.1 MHz.

Compound	δ (ppm)		
2a	12.93 (-NH)		
2b	9.79 (-CHO)		
1c	2.33 (-OCOCH$_3$)		
2c	2.80 (-NCOCH$_3$)		
1d	1.30 (-C(CH$_3$)$_3$)		
1f	8.17 ($H_{2'}$+$H_{6'}$);	7.43 ($H_{3'}$+$H_{4'}$+$H_{5'}$)	
1g	3.47 (-OSO$_2$-CH$_3$)		
1h	7.89 ($H_{2'}$+$H_{6'}$);	7.33 ($H_{3'}$+$H_{5'}$)	2.44 (-CH$_3$)
6	8.59 ($H_{6''}$);	7.97 ($H_{3''}$);	7.84 ($H_{4''}$)
	7.35 ($H_{5''}$)		
3a	6.55 (-OH)		
3c	2.29 (-OCOCH$_3$)		
3d	1.53 (-C(CH$_3$)$_3$)		
3f	8.27 ($H_{2'}$+$H_{6'}$);	7.63 ($H_{3'}$+$H_{4'}$+$H_{5'}$)	
3g	3.20 (-OSO$_2$CH$_3$)		
3h	7.62 ($H_{2'}$+$H_{6'}$);	7.38 ($H_{3'}$+$H_{5'}$);	2.44 (-CH$_3$)
9	4.40 (-NCH$_3$);	2.38 (-OCOCH$_3$)	
5a	9.94 (-NH)		
4c	2.30 (-OCOCH$_3$)		
5c	2.60 (-N-COCH$_3$)		
4d	1.57 (-C(CH$_3$)$_3$)		
4f	8.20 ($H_{2'}$+$H_{6'}$);	7.57 ($H_{3'}$+$H_{4'}$+$H_{5'}$)	
4g	3.20 (OSO$_2$CH$_3$)		
5g	3.23 (N-SO$_2$-CH$_3$)		
4h	7.75 ($H_{2'}$+$H_{6'}$);	7.33 ($H_{3'}$+$H_{5'}$);	2.42 (-CH$_3$)
5h	7.80 ($H_{2'}$+$H_{6'}$);	7.40 ($H_{3'}$+$H_{5'}$);	2.45 (-CH$_3$)
7	8.77 ($H_{2''}$+$H_{6''}$);	7.33 ($H_{3''}$+$H_{5''}$)	
8	9.00 ($H_{2''}$+$H_{6''}$);	8.10 ($H_{3''}$+$H_{5''}$);	7.51 ($H_{2'}$+$H_{6'}$)
	7.10 ($H_{3'}$+$H_{5'}$);	6.13 (-NH + -OH);	2.27 (-CH$_3$)
10	4.33 (-NCH$_3$);	2.38 (-OCOCH$_3$)	

both its O-and N-substituted derivatives.

Moreover, 3-hydroxypyridine resonances show a strong dependence on employed solvents (DMSO, D_2O and, in our spectra, $CDCl_3$); such a shift dependence was not found in the 3-O derivatives examined.

We believe that such differences support the already suggested betaine structure of 3a (not possible for compounds 3c-h), which would account for the strong solvent polarity dependence of the chemical shifts of its carbons atoms.

N-Methyl- and N-phenyl-3-pyridone exhibit a C-3 chemical shift very similar to that expected for a carbonyl carbon atom in this ring system (168 ppm); the chemical shift differences $\Delta\delta$ between the C-3 of the two 3-pyridones (DMSO-d_6 solutions) and the same carbon atom of unsubstituted pyridine is of the same magnitude as the $\Delta\delta$ observed between the C-4 of N-methyl-4-pyridone and the corresponding carbon atom of unsubstituted pyridine (about 42 ppm). This appear to support the hypothesis of the carbonyl nature of C-3 in the above N-substituted-3-pyridones.

^{13}C and ^{1}H assignment of substituent groups (Tables 4,5).

The ^{13}C resonance assignment of the carbon atoms of substituent groups was made essentially on the basis of the comparison with model compounds relevant to groups b, c, d, e, g, and were directly assigned by subtraction of the resonances of the pyridine moiety. Difficulties were met with groups f and h on account of superimposition of resonances with those of the pyridine ring. However, the perfect superimposition of carbon resonance of the tosyl groups in compounds 1h, 3h, 4h and 5h and of the benzoyl groups 1f, 3f and 4f allowed an unambiguous assignment to be made.

The assignment of carbon signals in compounds 6, 7 and 8 were made by comparing substituted pyridine and pyridone structures.

^{1}H resonance peaks of substituentes in compounds 1-10 were assigned by comparison with literature data and internal consistency.

I.R. SPECTROSCOPY

Whatever "mixing" of the pyridone carbonyl stretching with carbon-carbon ring double-bond stretching or pyridone ring vibrations actually occurs, it is a fact that all the N-substituted compounds (2, 5 and 7) show strong absorption bands between 1690 and 1610 cm^{-1}, which are lacking in the spectra of their related O-substituted compounds (1, 3, 4, 9 and 10) in which no absorption band between 1700 and 1600 cm^{-1} is present (Table 6). Also, the reported bands for 3-formyloxypyridine (1765, 1740, 1575 and 1474 cm^{-1}), for N-formyl-4-pyridone (1750, 1716, 1652 and 1636 cm^{-1}) [14], and for several N-acyl-4-pyridones and 4-acyloxypyridines [13] in CH_2Cl_2 are in full agreement with our results.

In contrast, it is noteworthy that of the reported carbonyl stretching modes for the N-methyl derivatives of 2-pyridone (1659 and 1538 cm^{-1}, $CDCl_4$ solution) [27], of 3-pyridone (1590 and 1512 cm^{-1}; $CDCl_3$ solution) [28] and of 4-pyridone (1575 and 1401 cm^{-1}, $CDCl_3$ solution) [29], only the first is quite close to the carbonyl stretching frequences of other N-substituted-2-pyridones. This results from the electron donor properties of the methyl group which enables the nitrogen lone pair electrons to restore ring aromaticity through an uneven charge distribution between the nitrogen

Table 6. I.R. characteristic bands (O.I M solutions), cm^{-1}.

Compound	ν OCOR NCOR	ν C=O pyridone C=C system	ν OSO_2R NSO_2R	hydroxypyridine or pyridone moiety
2a ($CDCl_3$)		1680,1665,1650 s,1610		1540,1470,1435,1375,1240,1090
2b "	1740 s, 1720	1690 vs,1620 vs		1545 s,1440,1390,1100
1c (CCl_4)	1830,1780,1770 vs			1590,1575,1468 s,1430,1370
2c "	1735	1690,1620		
1d ($CDCl_3$)	1800 s,1750 vs			1590,1465 s,1430 s,1395,1210 vs,1110 vs,1040
1e "	1800 vs,1770			1600 s,1590,1570,1460,1430 s,1340 s
1f "	1740 s			1590,1585,1572,1467,1450,1430,1265 s,1210 vs,1080 s,1060 s,1025 s
1g "			1370 vs,1170 vs	1595,1585,1470,1432 s
1h (CCl_4)			1380 vs,1180,1175 s	1590,1570,1465,1430 s,1090
6 ($CDCl_3$)		1670 vs,1610		1600,1590,1540,1470,1435 s,1270,1150
3a "				1500,1425,1290,1140
3c (CCl_4)	1770 vs			1590,1580,1475 s,1425 s,1370 s,1200 vs,1025 s,1010 s
3d ($CDCl_3$)	1750 vs			1590,1580,1475 s,1430 s,1400,1370,1210 vs,1125 vs,1030 s
3e "	1800 s,1775			1475,1430,1340,1230 s,1205 s,1170 vs,1110 s
3f "	1740 s			1472,1450,1425,1260,1210,1060,1025
3g "			1380 s,1170 vs	1580,1480,1430,1210
3h (CCl_4)			1390 vs,1180 vs	1600,1587,1578,1475 s,1425 s,1100 s,1025 s
9 (CD_3CN)	1790 vs			1510,1375,1185 vs
5a ($CDCl_3$)		1630		1510,1470,1380,1240 s,1180 s,1090 s
4c "	1770 s			1580,1495,1195 s
5c "	1750 s,1732	1650 vs,1630		1600,1400,1370,1245 vs,1175 vs,1070 s
4d "	1775 vs			1585 vs,1500,1480 s,1415,1400,1370,1280 s,1240 vs,1200 vs,1110 vs 1030 s
4e "	1800 vs,1755			1580 vs,1570 vs,1485 s,1410,1340 vs
4f "	1745 vs			1590 s,1500,1450,1415,1265 s,1230 s,1200 s,1080 s,1060 s,1030 s
4g "			1380 vs,1180 s,1170 s	1580 s,1495,1410
5g " (mixt.with 4g)		1655 s	1050 s	
4h ($CDCl_3$)			1380 vs,1175 vs	1600,1580 s,1490,1410,1095
5h "		1650 vs,1625	1385,1180 vs,1050 vs	1600,1470,1090
7 "		1650,1632 s		1580 vs,1490,1295,1190 s,1020
8 (DMSO-d_6)		1620 vs	1210 vs,1120 s	1583,1490 s,1355
10 (CD_3CN)	1840 s,1690			1565,1420,1320,1240 s,1220 vs,1060

and the oxygen atoms in N-methyl-3 and N-methyl-4-pyridones, with some polarization of the C=O bond.

The capability of the nitrogen lone pair to meet the electron demands of the pyridone systems seems to be supported by the position of the N-CO stretching bands in N-acyl-4-pyridone, which appear in the "ketonic" carbonyl 1750-1710 cm^{-1} region (refs. 2, 13, 14 and Table 6) rather than in the "amide" frequency range.

In the N-sulfonyl derivatives (5g and 5h) besides the characteristic sulfonamide ν_{SO_2} stretching bands at 1390-1370 and 1180-1170 cm^{-1}, a very intense absorption at 1050 cm^{-1} is present, while in the related O-sulfonyl derivatives (4g and 4h) no band is evident in the 1100-1000 cm^{-1} region, or only a medium intensity band at 1095 cm^{-1} is present. We are inclined to attribute the strong 1050 cm^{-1} band to an S=O stretching mode for the following reasons. Comparison of spectra of the p-toluenesulfonyl derivatives 4h and 5h reveals that the relative intensity of the asymmetrical ν_{SO_2} band at 1380 cm^{-1}, very strong for 4h, is greatly reduced in the spectrum of 5h, for which the 1050 cm^{-1} band is even stronger than the symmetrical ν_{SO_2} band at 1180 cm^{-1}. On the other hand, it is well known that the $\nu_{S=O}$ band of sulfoxides lies in a very small spectrum region at about 1050 cm^{-1} and is of a strong intensity, while sulfones are known to show two $\nu_{S=O}$ bands at 1350--1330 (asymmetric) and 1160-1120 cm^{-1} (symmetric): this bathochromic shift of the sulfoxides band in comparison with those of sulfones is attributed to the existence of the polarized $S^{+}-O^{-}$ form in the former [30]. No such band at 1050 cm^{-1} was observed, however, in the spectra of sulfonamides (bands at 1370-1330 and 1160-1120 cm^{-1}) [30,31], so that we are induced to conclude in favour of a peculiar "sulfonamide character" of 5g and 5h, which parallels the above mentioned lack of "amide character" of N-CO groups in N-acyl-4-pyridones.

CONCLUSION

^{13}C, ^{1}H-NMR and IR spectroscopies furnish consistent results in the study of the acyl-derivatives structure of the three hydroxy-pyridines.

Neither bulk nor electronic properties of the substituents appear to play any definitive role in determining the derivative structure. Moreover, from our data and from literature reports [1,2,13,14] the factors determining tautomeric equilibria in acyl 2- and 4-pyridones do not yet appear to have been identified.

EXPERIMENTAL

^{1}H-NMR spectra were obtain on a Varian T 60 spectrometer at 35° in $CDCl_3$ solutions. Spectra of 1a and 2b were also run on a Bruker WP 200 (200.1 MHz) and spectra of 1c, 2c, 3c, 4c, 5c, 1h, 6 and 3h on a Bruker WH-90 (90.1 MHz), in order to obtain ^{1}H-^{1}H coupling constants in the aromatic systems. Measurament conditions were as follows: WH-90: pulse width 1.3 μsec. (30° pulse), acquisition time 3.413 sec., spectral width 1200 Hz, number of data points 8 K, number of scans 20; WP-200: pulse width 3 μ sec. (40° pulse), acquisition time 6.55 sec., spectral width 2500 Hz, number of data points 32 K, number of scans 16.

^{13}C NMR spectra. Proton-decoupled ^{13}C NMR spectra were obtained at room temperature (28°) in a 10 mm. sample tube on a Bruker WH-90 instrument operating at 22.63 MHz in the Fourier Transform mode. The samples concentration was 100 mg/ml in $CDCl_3$ solutions, used as ^{2}H internal lock. Sample 8 was run in $(CD_3)_2SO$, samples 9 and 10 were run in CD_3CN. Measurament conditions were as follows: pulse width 4.5 μ sec. (30° pulse), acquisition time 1.365 sec., spectral width

6000 Hz, number of data points 16 K, number of scans 5000. ^{13}C chemical shifts were measured in ppm referred to internal TMS. All shifts reported were estimated to be accurate to ± 0.05 ppm. Proton-coupled spectra were obtained at "decoupler off". ^{1}H selective decoupling experiments were performed at 0.5 W power.

I.R. spectra were recorded as 0.1 M solutions with a Perkin-Elmer 580 spectrometer.

Melting points were determined on a Kofler hot stage and are uncorrected. All solvents and reagents were analytical grade and were used as received.

2-, 3-, and 4-hydroxypyridine were purchased from Fluka A.G. and melted respectively at 106-7°, 127-9° (recryst. from C_6H_6) and 148°C, the last having been purified as follows. The technical grade product was first made free from NaCl by extraction with warm $CHCl_3$. To the clear solution activated charcoal and anhydrous Na_2SO_4 were added, and the mixture was refluxed for 10 minutes. After filtration while hot through fluted filter paper, anhydrous Na_2SO_4 was again added to the $CHCl_3$ solution and the heating repeated. Solvent evaporation of the filtered solution gave a solid which was further dried by dissolving it in abs. ethanol-benzene 1:1 followed by distillation at normal pressure. The purified and dried product was stored in a vacuum dessicator over P_2O_5.
The following known compounds were prepared according to literature methods or with minor modifications: 2b [14]; 1c and 3c [32]; 5c [2]; 3e [33]; 4d and 4e [13]; 1f, 3f and 4f [15b]; 1h and 3h [15a]; 6 [16] and 7 [17]
The new compounds 2- and 3-pivaloyloxypyridines (1d, 3d) were prepared using the procedure described [13], from 2- or 3-hydroxypyridine, pivalic acid and dicyclohexylcarbodiimide in CH_2Cl_2: colourless liquids, obtained in a pure state after distillation in a Kugelrohr at 70-5°/1 mm.
2-pivaloyloxypyridine. Found: C,67.05; H,7.3; N,7.8; $C_{10}H_{13}NO_2$ requires C,67.0; H,7.3; N,7.8 %
3-pivaloyloxypyridine. Found: C,67.1; H,7.2; N,7.8 %

2-Trifluoroacetoxypyridine (1e).-2-Hydroxypyridine (1.0 g) was dissolved at room temp. in trifluoroacetic anhydride (5.0 g); the ester, immediately formed in practically quantitative yield, was purified by distillation in a Kugelrohr at 60°/0.3 mm as a colourless liquid and kept in a closed vessel at 20°.
(Found: C,43.75; H,2.3; N,7.3; $C_7H_4F_3NO_2$ requires C,44.0; H,2.1; N,7.3 %)

2-Methanesesulfonoxypyridine (1g).-2-Hydroxypyridine (1.0 g, 0.01 mole) and dried sodium bicarbonate (1.3 g, 0.015 mole) were stirred in abs. $CHCl_3$ (15.0 ml.) and allowed to react for ca 24 h. at room temp. with methanesulfonyl chloride (0.78 ml., 0.01 mole). The insoluble matter was then filtered and the clear solution evaporated under reduced pressure at room temp. The residue was first distilled at 128°/0.15 mm, then crystallized from n-hexane: m. p. 52-4°; yield 1.3 g (77 %).
(Found: C,41.8; H,4.2; N,8.3; $C_6H_7NO_3S$ requires C,41.6; H,4.1; N,8.1 %).

3-Metanesulfonoxypyridine (3g).-Through the above procedure from 3-hydroxypyridine (1.0 g, 0.01 mole) a solid product (1.6 g, 93 %) m.p. 57-9° (from n-hexane) were obtained.
(Found: C,41.8; H,4.3; N,8.0 %).

4-Methanesulfonoxypyridine (4g) and N-methanesulfonyl-4-pyridone (5g).-To 4-hydroxypyridine (50 mg, 0.53 mmole) and $NaHCO_3$ (66.0 mg, 0.79 mmole) suspended in $CDCl_3$ (2.0ml), methanesulfonylchloride (38.7 µl, 0.53 mmole) was added and the mixture stirred for 1 h. at room temp.: the filtered clear solution was examined by NMR and IR spectroscopy. The molar ratio of the two species 4g and 5g was at first about 2:1, but after a day a yellow resinous precipitate separated, and the only species remaining in solution was the ester 4g.
Attemps to isolate the compounds by solvent evaporation at 0°C under reduced pressure under N_2 were unsuccessful; only orange polymeric products were obtained.

4-(p-Toluenesulfonoxy)-pyridine (4g).-To a stirred suspension of 4-hydroxypyridine (1.0 g, 0.01 mole) in anhydrous pyridine (6.0 m), p toluenesulfonylchloride (2.0 g, 0.01 mole) was added at room temp. and the stirring was continued for 30 min. A quick initial dissolution of the hydroxypyridine was observed, followed by separation of a white solid. This was filtered and rinsed, first with anhydrous pyridine (about 2.0 ml), then with n-hexane: 1.1 g (42 %) raw product, m.p. 70-8° were obtained, which was crystallized from warm n-hexane (at no more than 50°) as colourless needles, 150-60° (lit. [15a] m.p. >70°) then resolidified and remelted at 221-3°. DSC analysis showed an exothermic phase transition at 80°, two minor ones at 133° and 144°, followed by two endothermic transition at 173° and 223°.
(Found: C,57.6; H,4.3; N,5.45; $C_{12}H_{11}NO_3S$ requires C,57.8; H,4.45; N,5.6 %)
The thermal decomposition product was identified as 1-(4'-pyridyl)-4-hydroxypyridinium ditosylate (8), by comparison with an authentic sample prepared from 1-(4'-pyridyl)-4-pyridone, and two moles of p-toluenesulfonic acid; m.p. 226° (DSC), from n-butanol.

N-(p-Toluenesulfonyl)-4-pyridone (5h).-To a stirred suspension of 4-Hydroxypyridine (1.0 g, 0.01

mole) and $NaHCO_3$ (1.3 g, 0.015 mole) in abs. $CHCl_3$ (15.0 ml) p-toluenesulfonylchloride (2.0 g, 0.01 mole) was added at room temp., and the mixture was stirred overnight. To the filtered clear solution n-hexane (ca 30 ml) was added until turbidity occurred.
After about 1h, the crystals were rapidly collected, rinsed with n-hexane and dried at room temp. over P_2O_5. White leaflets m.p. 45-50° (0.1 g) which rather rapidly decomposed to a blue-brownish solid.
(Found: C,57.5; H,4.5; N,5.6; $C_{12}H_{11}NO_3S$ requires C, 57.8; H,4.45; N,5.6 %)

3-Acetoxy-N-methylpyridinium iodide (9).-A solution of 3-acetoxypyridine 3c [32] (1.0 g) and excess methyl iodide (1.0 ml) in acetone (10.0 ml) was allowed to react at room temperature in the dark for 24 hours. The separated white prisms (1.5 g, 73.7 %), crystallized from acetone, had m.p.120-2°.
(Found: C,34.4; H,3.6; N,5.2; I,45.5; $C_8H_{10}INO_2$ requires C,34.4; H,3.6; N,5.0; I,45.5 %)

4-Acetoxy-N-methylpyridinium iodide (10).-To a suspension of N-acetyl-4-pyridone [2] (5c) m.p. 125-35° (1.0 g) in abs. chloroform (10.0 ml) excess methyl iodide (1.0 ml) was added and the mixture kept in the dark for 48 hours at room temp. with occasional shaking. Glistening white leaves separated, m.p. 140-5°, which were collected, rinsed with abs. ether and crystallized by dissolution in warm (no more than 40°) anhydrous CH_3CN and addition of 3-4 volumes of anhydrous 2-butanone. Yield 0.8 g (39.3 %) m.p. 151-5°.
(Found: C,34.7; H,3.7; N,4.8; I,45.5 %).

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