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A CARBON-13 AND PROTON NUCLEAR MAGNETIC RESONANCE STUDY OF HYDROXY- AND MERCAPTO-NITROPYRIDINES AND THEIR N-, O- AND S-METHYL DERIVATIVES AND ANALOGOUS COMPOUNDS IN DIMETHYL SULFOXIDE

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Abstract — Carbon-13 and proton n.m.r. spectra of hydroxy- and mercapto-nitropyridines and their N-, O- and S-methyl derivatives and analogous compounds have been measured in (D6)dimethyl sulfoxide. Carbon-13 n.m.r. spectroscopy, in contrast to ^1H n.m.r. spectroscopy, has been shown to provide a clear distinction between O-methyl and nuclear N-methyl groups. Methoxy groups were found to occur in the range δ 52.80 to 57.18, nuclear N-methyl groups at 33.59-43.56, and methylthio groups at 12.00-14.65 for the compounds examined in (D6)dimethyl sulfoxide. 3-Nitropyridine-4-thiol† unlike its oxygen analogue, 3-nitropyridin-4-ol† appears to exist in the thiol form.

In a recent paper[1] we reported that ^{13}C n.m.r. spectroscopy in $CDCl_3$ gave a clear distinction between O- and N-methyl groups in nitrogen heterocyclic systems for which ^1H n.m.r. did not provide a clear distinction. It was found that the

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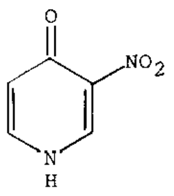
† Throughout this paper, such names as 'pyridine-4-thiol' (and similarly 'pyridin-4-ol') will be used without implying that the tautomer with an SH group is necessarily present in more than a trace quantity at equilibrium.

resonance signal due to the carbon of the methoxy group occurred in the range δ 53.0-61.87 and that of the *N*-methyl group was in the range 34.29-49.62 for the variety of compounds examined. In this paper we examine the ^{13}C and ^{1}H n.m.r. spectra of nitropyridinols and nitropyridinethiols (which were not soluble in $CDCl_3$) as well as their *N*-, *O*- and *S*-methyl derivatives and analogous compounds (for comparison) in dimethyl sulfoxide.

The ^{1}H n.m.r. spectra (Table 1 and data contained in the references of the Experimental section) showed that in derivatives of the pyridinols, the *N*-methyl group was in the range δ 3.43-3.77 and that of the methoxy group was in the range 3.82 (for 4-methoxypyridine) to 4.05. These spectra also revealed that 3- and 5-nitropyridin-2-ol and 3-nitropyridin-4-ol, like pyridin-2- (and 4-)ol[2], showed close similarity to their respective *N*-methyl derivatives rather than the *O*-methyl analogues. This clearly indicated quinonoid type structures such as (1) for these compounds in dimethyl sulfoxide [*cf*. ionization constant and u.v. spectral data for (1) in water[3]]; but no quantitative calculations of tautomeric ratios were made due to the limitations of the method.



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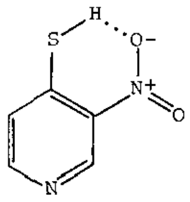

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Amongst the sulfur analogues 1-methyl-3-nitropyridine-2 (and 4)-thiones could not be prepared for study but 3- and 5-nitropyridine-2-thiol showed distinct differences in their ^{1}H n.m.r. compared to their respective *S*-methyl derivatives. In contrast, 3-nitropyridine-4-thiol did not show such differences from its *S*-methyl derivative (see below).

Proton coupling constants for 3-nitropyridin-2-ol were similar to those of its *N*-methyl derivative and different from that of its methoxy analogue. This pattern applied generally to the hydroxy and mercapto compounds excepting that the coupling constants for 3-nitropyridine-4-thiol were similar to those of the *S*-methyl derivative.

The ^{13}C n.m.r. spectra (Table 2) of the nitro compounds in dimethyl sulfoxide indicated, as previously[1], a clear distinction between *N*- and *O*-methyl groups. In

Table 1. ^{1}H n.m.r. spectra in CD_3SOCD_3

Compound	H2	H3	H4	H5	H6	NMe	OMe	SMe	J(Hz)
Pyridine									
2-OH-3-NO_2			8.43	6.38	7.88				$J_{4,5}$ 7.6 $J_{4,6}$ 2.1, $J_{5,6}$ 6.2
1-Me-3-NO_2-2=O			8.39	6.41	8.23	3.58			$J_{4,5}$ 7.7 $J_{4,6}$ 2.1, $J_{5,6}$ 6.6
2-OMe-3-NO_2			8.48	7.25	8.51		4.03[a]		$J_{4,5}$ 7.9, $J_{4,6}$ 1.8, $J_{5,6}$ 4.9
2-OH-5-NO_2		6.43	8.12		8.65				$J_{3,4}$ 10.1, $J_{3,6}$ 0.5, $J_{4,6}$ 3.2
1-Me-5-NO_2-2=O		6.47	8.13		9.18	3.56			$J_{3,4}$ 10.0, $J_{3,6}$ 0.5, $J_{4,6}$ 3.2
2-OMe-5-NO_2		7.04	8.48		9.09		4.01[a]		$J_{3,4}$ 9.1, $J_{3,6}$ 0.6, $J_{4,6}$ 2.9
4-OH-3-NO_2	8.80			6.50	7.79				$J_{2,6}$ 1.6, $J_{5,6}$ 7.5
1-Me-3-NO_2-4=O	8.91			6.50	7.76	3.77			$J_{2,6}$ 2.2, $J_{5,6}$ 7.7
4-OMe-3-NO_2	8.98			7.45	8.70		4.05[a]		$J_{2,6}$ 0, $J_{5,6}$ 5.9
2-SH-3-NO_2			7.94	6.90	8.14				$J_{4,5}$ 6.2, $J_{4,6}$ 1.7, $J_{5,6}$ 7.7
2-SMe-3-NO_2			8.60	7.44	8.84			2.55	$J_{4,5}$ 8.3, $J_{4,6}$ 1.6, $J_{5,6}$ 4.6
2-SH-5-NO_2		7.32	7.98		8.56				$J_{3,4}$ 9.6, $J_{3,6}$ 0.5, $J_{4,6}$ 2.7
2-SMe-5-NO_2		7.57	8.38		9.22			2.62	$J_{3,4}$ 8.9, $J_{3,6}$ 0.7, $J_{4,6}$ 2.7
4-SH-3-NO_2	9.42			7.90	8.70				$J_{2,5}$ 0.4, $J_{2,6}$ 0, $J_{5,6}$ 5.6
4-SMe-3-NO_2	9.25			7.61	8.67			2.59	$J_{2,5}$ 0.5, $J_{2,6}$ 0.2, $J_{5,6}$5.6
2-SH[b,c,d,e.]		7.32	7.42	6.76	7.67				c,d,e.
1-Me-2=S[d]		7.45	7.35	6.78	8.16	3.86			d
2-SMe[e]		7.28	7.64	7.09	8.44			2.51	d

Table 1. (Cont.)

Compound	H2	H3	H4	H5	H6	NMe	OMe	SMe	J(Hz)
4-SH[e]	7.65	7.22		7.22	7.65				e
1-Me-4=S	7.55	7.15		7.15	7.55	3.72			$J_{2,3}$ 7.1, $J_{5,6}$ 7.1
4-SMe	8.37	7.24		7.24	8.37			2.51	$J_{2,3}$ 4.5, $J_{3,5}$ 1.6, $J_{5,6}$ 4.5
Pyrimidine									
2-OH			8.28	6.37	8.28				$J_{4,5}$ 5.1, $J_{5,6}$ 5.1
1-Me-2=O			8.52	6.40	8.18	3.43[a]			$J_{4,5}$ 4.2, $J_{4,6}$ 2.9, $J_{5,6}$ 6.5
2-OMe			8.62	7.14	8.62		3.92		$J_{4,5}$ 4.8, $J_{5,6}$ 4.8
2-SH			8.26	6.83	8.26				$J_{4,5}$ 5.2, $J_{5,6}$ 5.2
1-Me-2=S			f	f	f	3.81			f
2-SMe			8.65	7.21	8.65			2.53	$J_{4,5}$ 4.9, $J_{5,6}$ 4.9

[a] Irradiation of the methyl group sharpens the signals of H2 and H6.

[b] Chemical shifts from D. W. Aksnes and H. Kryvi, Acta. Chem. Scand., 1972, 26, 2255.

[c] Coupling constants have been reported by M. C. Vitorge, M. T. Chenon, C. Coupry, and N. Lumbroso-Bader, Org. Magn. Reson., 1983, 21, 20.

[d] Coupling constants have been reported by D. W. Aksnes and H. Koyvi, Acta. Chem. Scand., 1972, 26, 2255.

[e] Coupling constants have been reported by A. Schanck, J. M. Dereppe and M. Van Meerssche, Bull. Soc. Chim. Belg., 1983, 92, 199.

[f] Complex at 270 mHz.

Table 2. ^{13}C n.m.r. spectra in CD_3SOCD_3

Compound	C2	C3	C4	C5	C6	NMe	OMe	SMe
<u>Pyridine</u>								
2-OH-3-NO_2	159.95	154.26	140.01	103.69	143.21			
1-Me-3-NO_2-2=0	154.99	154.07	138.55	103.01	146.87	37.89		
2-OMe-3-NO_2	155.56	133.95	135.30	117.34	151.91		54.53	
2-OH-5-NO_2	162.04	118.97	134.14	130.12	138.58			
1-Me-5-NO_2-2=0	161.41	117.61	133.30	129.56	142.51	37.68		
2-OMe-5-NO_2	166.91	111.19	134.52	139.47	144.51		54.69	
4-OH-3-NO_2	139.61	138.36	168.24	122.30	137.79			
1-Me-3-NO_2-4=0	143.53	137.50	167.25	122.84	141.88	43.56		
4-OMe-3-NO_2	146.03	136.46	158.27	109.78	154.94		57.18	
2-SH-3-NO_2	169.11	152.64	132.81	111.54	141.83			
2-SMe-3-NO_2	156.83	141.94	134.11	119.54	153.72			13.76
2-SH-5-NO_2	183.16	132.92	128.91	135.57	137.55			
2-SMe-5-NO_2	167.91	120.97	130.99	141.02	144.59			13.22
4-SH-3-NO_2	146.98	142.32	144.10	120.84	153.72			
4-SMe-3-NO_2	146.46	141.42	149.28	120.40	152.28			14.65
2-SH	177.75	132.92	137.28	112.58	137.74			
1-Me-2=S	178.94	134.19	134.57	112.95	142.42	44.96		
2-SMe	159.16	121.03	136.36	119.37	149.25			12.59

Table 2. (Cont.)

Compound	C2	C3	C4	C5	C6	NMe	OMe	SMe
Pyrimidine								
2-OH	156.43		156.94	103.47	156.84			
1-Me-2=O	156.05		165.66	103.42	150.39	38.30		
2-OMe	165.04		159.49	115.36	159.49		54.31	
4-OH[a]	150.36		161.09	115.80	153.88			
3-Me-4=O	152.96		160.57	114.42	153.53	33.59		
1-Me-4=O	153.29		168.86	110.87	145.53	39.63		
4-OMe	158.24		168.75	108.27	157.48		53.27	
2-SH[b]	181.20		154.00	109.20	154.00			
1-Me-2=S	185.44		159.46	109.38	150.79	45.97		
2-SMe	171.49		157.54	116.91	157.54			13.41
4-SH	149.73		182.82	128.32	149.86			
3-Me-4=S	152.69		183.29	128.50	147.49	40.97		
1-Me-4=S	148.38		197.80	125.15	137.83	39.74		
4-SMe	157.78		170.13	118.53	154.80			12.00

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[a] Similar values have been reported by G. W. H. Cheeseman, C. J. Turner and D. J. Brown, *Org. Magn. Reson.*, 1979, **12**, 212.

[b] Data from C. J. Turner and G. W. H. Cheeseman, *Org. Magn. Reson.*, 1976, **8**, 357.

the compounds examined, the nuclear _N_-methyl group was found to occur in the range 33.59-43.56, the _O_-methyl group in the range 52.80 (for 2-methoxypyridine) to 57.18, and methylthio groups at 12.00-14.65. Carbon-13 n.m.r. was more useful than ^{1}H n.m.r. in the study of tautomerism, with the signal due to C5 showing the clearest differences between fixed tautomeric forms: the signal in aromatic systems was consistently different from that in quinonoid systems. For example, the signal for C5 in 3-nitropyridin-2-ol was at 103.69, its _N_-methyl derivative at 103.01 and its _O_-methyl analogue at 117.34, thus clearly indicating that the former exists as the pyridinone. Likewise for 3-nitropyridin-4-ol and its _N_- and _O_-methyl derivatives the values were 122.30, 122.84 and 109.78 respectively. With the exception of 3-nitropyridine-4-thiol, which is discussed below, the signal due to C5 in all the hydroxy and mercapto compounds examined differed from that of the corresponding _O_- or _S_-methyl derivative by from 5.45 to 13.65 ppm.

Although the _N_-methyl derivative of 3-nitropyridine-4-thiol was not available, the signal for C5 in the parent compound and _S_-methyl derivative was at 120.84 and 120.40 respectively which strongly suggests, like the ^{1}H n.m.r. and $J_{2,6}$ coupling constants that this compound exists as the thiol (2).

Comparison of the ^{1}H n.m.r. signal due to the _N_-methyl group in the pyridines shows that when in the γ-position to the oxo group, it was downfield by 0.20 ± 0.01 ppm relative to the α-isomers, and in the pyrimidines by 0.13-0.14 ppm. The corresponding ^{13}C n.m.r. signals were also downfield by 5.7 ± 0.1 and 3.6 ± 2.5 ppm respectively. The _N_-methylpyridinethiones and pyrimidinethiones showed the reverse behaviour in the ^{1}H n.m.r. with the γ-isomer upfield by 0.19-0.14 ppm, and the ^{13}C n.m.r. being variable.

EXPERIMENTAL

The ^{13}C and ^{1}H n.m.r. spectra were measured on a Jeol FX90Q spectrometer with digital resolution of 0.12 Hz at 30°, tetramethylsilane being used as internal standard. Spectra were measured in (D6)dimethyl sulfoxide and ^{13}C n.m.r. spectra at concentrations of 0.060-0.070 g/ml, unless specified otherwise. Reasonable spectra were obtained after the accumulation of 300-500 FID values.

Assignment of carbon-13 resonances was confirmed by selective decoupling of the proton spectra.

Compounds required for this work were prepared by literature procedures as reported previously[1] and as folows: 3-nitropyridin-2-ol,[4] 2-methoxy-3-

nitropyridine,[5] 1-methyl-3-nitropyridin-2-one,[6] 3-nitropyridin-4-ol,[7] 4-methoxy-3-nitropyridine,[8] 1-methyl-3-nitropyridin-4-one,[9] 5-nitropyridin-2-ol,[10] 2-methoxy-5-nitropyridine,[11,12] 1-methyl-5-nitropyridin-2-one,[13] 3-nitropyridine-2-thiol,[14] 2-methylthio-3-nitropyridine,[14] 5-nitropyridine-2-thiol,[10,15] 2-methylthio-5-nitropyridine,[14] 3-nitropyridine-4-thiol,[16] and 4-methylthio-3-nitropyridine.[14] Some ^{1}H and ^{13}C n.m.r. spectra of reference compounds in (D6)dimethyl sulfoxide have been recorded in the literature and are not shown in the Tables. These include the ^{1}H n.m.r. of pyridin-2- (and 4-)-ol,[2] their *N*- and *O*-methyl derivatives,[2] pyrimidin-4-ol and pyrimidine-4-thiol and their *N*-, *O*- and *S*-methyl derivatives[17] and the ^{13}C n.m.r. of pyridin-2-ol[2,18] and its *N*- and *O*-methyl derivatives[2] (the *N*-methyl signal in 1-methylpyridin-2-one is now revised to 36.65), pyridin-4-ol[2] and its *N*-and *O*-methyl derivatives,[2] pyridine-4-thiol[19] and its *N*- and *S*-methyl derivatives[19]. 1-Methyl-3-nitropyridine-4-thione (required for n.m.r. comparison with the unmethylated mercapto compound) could not be prepared by reaction of 1-methyl-3-nitropyridin-4-one with phosphorus pentasulfide in pyridine, and 4-methoxy-3-nitropyridine with methyl iodide in nitromethane did not give 4-methoxy-3-nitropyridine methiodide (required for reaction with potassium hydrogen sulphide) but instead gave the rearranged product 1-methyl-3-nitropyridin-4-one.

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