NITRATION OF 6-HYDROXY-1-METHYLPYRIDIN-2-ONE

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Abstract - Classical conditions of nitration applied to the 6-hydroxy-1-methylpyridin-2-one lead to the dimerisation of the compound following a Michael addition-type mechanism. This paper deals with the structure of this product determined by NMR studies.

INTRODUCTION

The synthesis of 6-hydroxy-1-methyl-3-nitropyridin-2-one was reported for the first time in 1970.[1] In our hands, the formation of this molecule was never observed but a compound with a molecular weight twice that of the expected nitro compound was identified. We report here the data assuming its structure.

EXPERIMENTAL

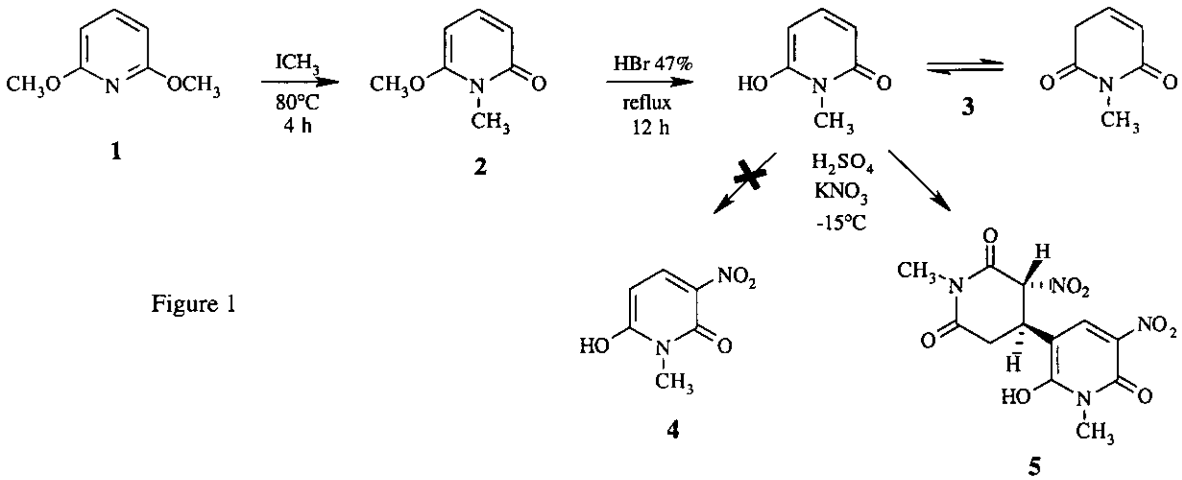


Figure 1

Pyridone (**2**) was obtained *via* a *N*-methylpyridinium intermediate made with methyl iodide, which enhanced the subsequent *O*-demethylation according to a previously reported synthesis route.[2,3]

Compound (**3**) was prepared by demethylation of the second methoxy group in 47% aqueous HBr for 12 h at 140°C. Reaction conditions were little modified when compared to the method previously described.[2] Nitration of this compound was carried out in concentrated sulfuric acid at -15°C with potassium nitrate.[1] Formation of compound (**4**) was not observed but rather that of a compound whose MS showed a molecular ion peak at m/z=340 instead of m/z=170. Structure elucidation was obtained by ^{1}H and ^{13}C NMR.

METHODS

NMR sample preparation.

The NMR spectra were recorded with a 5 mM solution of **5** in DMSO-d_6.

NMR spectroscopy.

All the spectra were acquired at 300 K on a Brüker DRX-400 spectrometer, equipped with a triple-resonance probehead containing a self-shielded z-gradient coil. In all NMR experiments, pulsed field gradients were applied where appropriate and as previously described[4] to facilitate the suppression of spectral artefacts. Quadrature detection in the indirectly detected dimension was accomplished by using the States-TPPI method.[5] The data was processed and analysed on a Silicon Graphics computer using Brüker XWINNMR software.

^{1}H and ^{13}C resonances of compound (**5**) were assigned thanks to analysis of sensitivity-enhanced ^{13}C HSQC[6] and ^{13}C HMBC.[7] The assignments made from these experiments were consistent with the crosspeaks observed in COSY-DQF[8] and ROESY[9] (mixing time : 250 ms) spectra.

The analyses of the coupling constants ($^{2,3}J_{HH}$ observed by COSY, $^{1,2,3,4}J_{HC}$ by HSQC and HMBC) and the NOE (observed by ROESY) made it possible to assign all hydrogens and carbons (Table 1). Spectral investigation (Table 2) led unequivocally to the following structure (Figure 2) resulting from a Michael addition of the tautomeric form of pyridone **4** to the C_3-C_4 double bond activated by the nitro group :

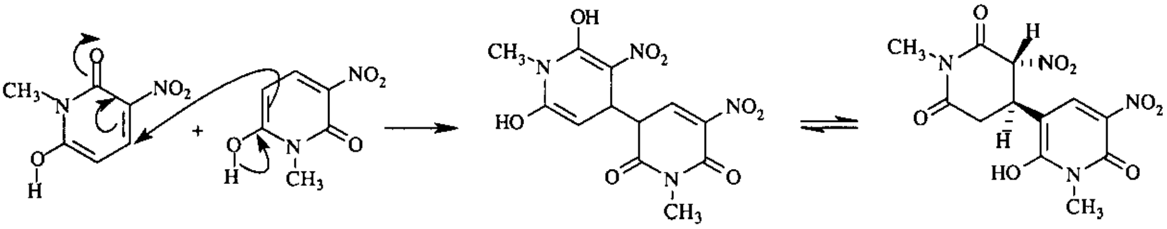
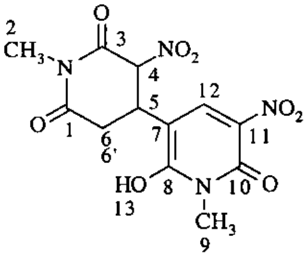


Figure 2

^{1}H and ^{13}C NMR have allowed to assign relative stereochemistry and favored conformation of compound (**5**) on the basis of coupling constant values. J value (J = 13 Hz) between the protons at position C4 and C5 of the heterocycle indicates that the preferred conformation of compound (**5**) in DMSO-d_6 solution is



	^{1}H NMR			^{13}C NMR
	δ_H	multiplicity	J (Hz)	δ_C
1	-	-	-	170.2
2	3.04	s	-	26.4
3	-	-	-	165.8
4	6.57	d	13	88.0
5	3.92	dt	4.5 and 13	37.0
6	2.76	dd	4.5 and 17	34.8
6'	3.29	dd	13 and 17	34.8
7	-	-	-	104.6
8	-	-	-	162.9
9	3.10	s	-	25.8
10	-	-	-	156.8
11	-	-	-	ni
12	7.99	s	-	135.2
13	10.6	br s	-	-

ni non identified

Table 1

NOE	$^3J_{HC}$
	H 2 - C 1
	H 2 - C 3
	H 4 - C 7
	H 6 - C 7
	H 5 - C 1
H 4 - H 12	H 5 - C 3
H 5 - H 12	H 5 - C 8
	H 5 - C 12
	H 9 - C 8
	H 9 - C 10
	H 12 - C 5
	H 12 - C 8
	H 12 - C 10

Table 2

4,5-dipseudoaxial. J value of 4.5 Hz shows the coupling between H5 and H6 (pseudoequatorial). J = 13 Hz indicates the coupling between H5 and the second proton H6 (pseudoaxial). Then J = 17 Hz is the coupling constant of the geminal protons H6-H6'. Thus the conclusion is that compound (**5**) is the 4,5-*trans* isomer and has the 4*R*,5*R* configuration (Figure 3).

Figure 3

All these results have enabled us to conclude that it is not possible to prepare the 6-hydroxy-3-nitropyridin-2-one by the method previously described. Moreover, in this paper, we have provided evidence that the nitration of the 6-hydroxypyridin-2-one heterocycle really occurred at 3-position of the pyridone.

EXPERIMENTAL

Synthesis of 6-methoxy-1-methylpyridin-2-one (**2**)

2,6-Dimethoxypyridine (4.75 g ; 35.9 mmol) was heated with methyl iodide (6.3 mL ; 100.6 mmol) for 24 h at 80°C (sealed tube). The methyl iodide was distilled off and the residue treated in petroleum ether to yield the methoxy derivative. Crystallisation from ethyl acetate/petroleum ether as needles (3.6 g, 72% yield), mp : 52-54°C. TLC (CH_2Cl_2/MeOH 95/5) : Rf : 0.57. IR (KBr) : 3397 (CH aryl) ; 1652 (C=O). MS (electronic impact) : 140 (100%) ; 125 (8%) ; 97 (4%).

Synthesis of 6-hydroxy-1-methylpyridin-2-one (**3**)

The foregoing methoxy compound (5 g ; 36 mmol) was heated at reflux with 47% hydrobromic acid (120 mL) for 12 h. The reaction mixture was cooled, brought to pH 3 by the addition of 27% aqueous ammoniac and extracted with chloroform. The organic layers were dried on $MgSO_4$. Evaporation of the extracts yield the hydroxy derivative. Crystallisation from ethyl acetate/petroleum ether as a white powder (4.1 g, 92% yield), mp : 161-164°C. TLC (CH_2Cl_2/MeOH 95/5) : Rf : 0.52. IR (KBr) : 1653 (C=O). ^1H NMR (DMSO-d_6) shows two tautomer forms : 6-hydroxy-1-methylpyridin-2-one and 1-methylpyridine-2,6-dione with a 2:1 ratio. More intense set : 3.28 (s, 3H, N-CH_3) ; 5.65 (d, 2H, J = 8 Hz, H_3 and H_5) ; 7.22 (t, 1H, J = 8 Hz, H_4) ; no OH signal observed. Less intense set : 3.05 (s, 3H, N-CH_3) ; 3.51 (s, 2H, α-CH_2) ; 6.19 (m, 1H, $J_{\beta\gamma}$, γ-CH) ; 6.19 (m, 1H, $J_{\beta\gamma}$, β-CH). After addition of D_2O the signals at 6.19, 5.65 and 3.51 disappeared, and those at 7.22 and 6.91 became singlets. MS (electronic impact) : 126 (100%) ; 118 (3%) ; 100 (13%) ; 97 (2%).

Synthesis of 6-hydroxy-1-methyl-4-(1-methyl-3-nitro-2,6-dioxopiperidinyl)-3-nitropyridin-2-one (**5**)

6-Hydroxy-1-methylpyridin-2-one (1 g ; 8 mmol) was dissolved in sulfuric acid (20 mL) at -15°C. Potassium nitrate (1.05 g ; 10.4 mmol) was added slowly to this solution. After 20 min, the whole was poured on ice, and the separated nitro derivative was collected. Crystallisation from water as a yellow powder (2.1 g, 79% yield), mp : 165°C (decomp). TLC (CH_2Cl_2/MeOH 8/2) : Rf : 0.41. IR (KBr) : 1740 (C=O) ; 1671 (C=O) ; 1627 (C=N) ; 1563 and 1364 (C-NO_2). MS (electronic impact) : 340 (68%) ; 293 (100%) ; 276 (25%) ; 246 (14%) ; 209 (25%) ; 192 (31%) ; 170 (47%) ; 149 (20%) ; 126 (14%) ; 105 (9%) ; 58 (9%).

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