^{13}C NMR Studies of Tautomerism in Imidazo[4,5-*c*]pyridines

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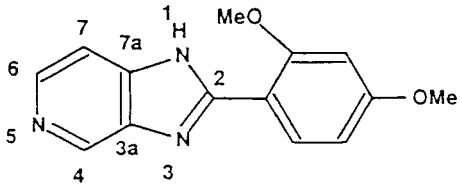
A detailed analysis of the ^{13}C NMR spectra of the 1-*N*- and 3-*N*-methyl derivatives of 1*H*-2-(2,4-dimethoxyphenyl)imidazo[4,5-*c*]pyridine, utilizing long-range couplings and 2D ^{1}H–^{13}C correlation experiments, has led to an unambiguous assignment of all carbons. Comparison of these definitive assignments of C-3a and C-7a, in particular, with those of the tautomers of 1*H*-2-(2,4-dimethoxyphenyl)imidazo[4,5-*c*]pyridine has permitted confirmation of the predominance of the 1*H*-tautomer for the latter. In addition, previous conflicting assignments for 1*H*-imidazo[4,5-*c*]pyridine and its 3-*N*-methyl derivative are now resolved. Revision of these assignments leads to the conclusion that the 1*H*-tautomer of 1*H*-imidazo[4,5-*c*]pyridine is predominant.

KEY WORDS ^{13}C NMR Tautomerism Inotropism Imidazopyridine

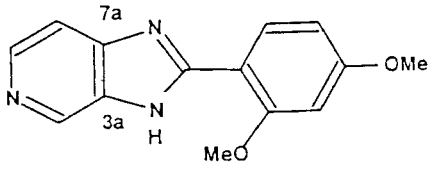
INTRODUCTION

We have recently completed a ^{13}C NMR study[1] of the protonation equilibria and tautomerism of cardiotonic sulmazole analogues such as **1**.

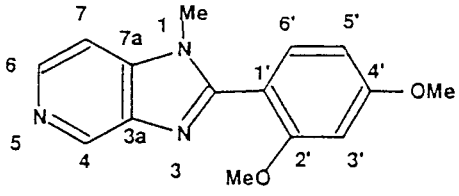
During this investigation it became apparent that inconsistencies existed between ^{13}C assignments of C-3a and C-7a for **1b** and those previously reported[2,3] for 1*H*-imidazo[4,5-*c*]pyridine and its 3-*N*-methyl derivative. These ^{13}C assignments are often important for determining the major tautomers of imidazo[4,5-*c*]pyridines and we therefore required an unambiguous assignment of C-3a and C-7a in suitable reference compounds. A detailed investigation of the ^{1}H and ^{13}C parameters for 1-*N*- and 3-*N*-methyl-2-(2,4-dimethoxyphenyl)imidazo[4,5-*c*]pyridine (**2** and **3**), respectively, was therefore undertaken, as in these cases no tautomerism is possible.



1a



1b



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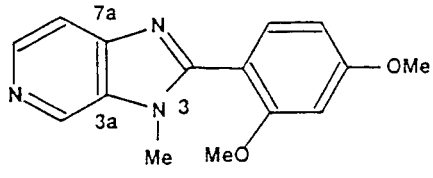

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EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were obtained at 360 and 90 MHz, respectively, on a Bruker AM360 spectrometer. ^{13}C spectra were measured both with and without proton decoupling. Two-dimensional ^{1}H–^{13}C correlated spectra were collected, optimized both for one-bond carbon–proton couplings (*ca.* 170 Hz) and for longer range carbon–proton couplings (*ca.* 6 Hz). The two NMe analogues (**2**, **3**) were studied as DMSO-d_6 solutions at 30 °C. $CD_3 \cdot SOCD_2H$ was used as an internal chemical shift reference for ^{1}H NMR (δ2.5), and $(CD_3)_2SO$ as chemical shift reference for ^{13}C NMR (39.6 ppm from Me_4Si).

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SYNTHESIS

2-(2,4-Dimethoxyphenyl)-3-methylimidazo[4,5-*c*]pyridine hydrochloride (3)

4-Amino-3-methylaminopyridine (2.46 g, 0.02 mol) and 2,4-dimethoxybenzoic acid (3.64 g, 0.02 mol) were pulverized together to a fine powder and then added in portions to phosphoryl chloride (60 ml) containing pyrophosphoryl tetrachloride (0.5 ml) with stirring.

The mixture was heated at reflux under nitrogen for 7 h, cooled to 0 °C and then poured onto diethyl ether (250 ml). The resulting solid was collected by filtration, dissolved in chloroform and the solution washed with aqueous saturated sodium bicarbonate solution. After washing with water and drying, the organic layer was evaporated. Chromatography of the residue on silica and elution with chloroform–methanol (9:1) gave the desired product. This was recrystallized from benzene–hexane and converted to the hydrochloride by treatment with ethereal hydrogen chloride to give 1.83 g (30%) of **3** · hydrochloride (m.p. 235–237 °C). Analysis found: C, 58.9; H, 5.40; N, 13.4; Cl, 11.8. $C_{15}H_{15}N_3O_2$ · HCl requires C, 58.8; H, 5.27; N, 13.7; Cl, 11.6%.

2-(2,4-Dimethoxyphenyl)-1-methylimidazo[4,5-*c*]pyridine dihydrochloride (2)

3-Amino-4-methylaminopyridine, 2,4-dimethoxybenzoic acid, phosphoryl chloride and pyrophosphoryl tetrachloride were reacted together in a manner analogous to that used above to give a 15% yield of **2** · dihydrochloride (m.p. 225–227 °C). Analysis found: C, 52.4; H, 5.21; N, 11.9; Cl, 20.6. $C_{15}H_{15}N_3O_2$ · 2HCl requires C, 52.6; H, 4.97; N, 12.3; Cl, 20.8%.

RESULTS AND DISCUSSION

The ^{1}H NMR signals of **2** and **3** were readily assigned by inspection on the basis of chemical shifts and coupling constants. ^{1}H–^{1}H NOE values confirmed the position of the NMe in each compound. Two-dimensional ^{1}H–^{13}C correlation experiments optimized for ^1J(CH) aided assignment of the ternary carbons, and those adjusted to longer range J(CH) aided assignment of the quaternary carbons. In particular, the relative assignments of C-3a and C-7a were quite distinct, since spin coupling from NMe protons was only observed over three bonds to C-2 and C-7a in **2** and to C-2 and C-3a in **3**. Long-range carbon–proton couplings quoted in Table 1 were measured from proton-coupled ^{13}C spectra or, in some cases, from selectively decoupled spectra to simplify the C-3a and C-7a multiplets.

On this basis, for compound **2**, C-3a resonated at 139.9 ppm and C-7a at 140.4 ppm, while for compound **3**, C-3a was assigned to the signal at 133.8 ppm and C-7a at 147.2 ppm. The long-range coupling and 2D correlation experiments described above provided definitive assignments for all carbons of compounds **2** and **3**.

Having firmly established the assignments of C-3a and C-7a for compounds **2** and **3**, we now re-examined

Table 1. ^{13}C chemical shifts (ppm)

	1a (major)	1b (minor)	2	3	4[b]	4[c]	5[c]	6[c]
C-2	150.8	152.0	153.5	154.7	146.4	148.1	148.9	150.3
C-4	140.6	134.7	141.2	133.7	139.0	140.8	143.1	135.3
C-6	140.9	140.9	141.2	141.2	141.0	142.8	142.6	143.0
C-7	107.0	112.8	105.8	113.5	110.7	112.5	108.5	116.2
C-3a	139.2[a]	132.6	139.9	133.8	137.3	139.1	141.4	133.9
C-7a	140.2[a]	147.3	140.4	147.2	142.4	144.0	141.4	149.6
C-1′	110.2	110.2	111.0	110.8				
C-2′	162.7	162.7	162.6	162.7				
C-3′	98.6	98.6	98.6	98.6				
C-4′	158.5	158.5	158.6	158.5				
C-5′	106.5	106.5	105.8	105.9				
C-6′	131.3	131.3	132.9	132.9				
2′-OMe			55.6[a]	55.6[a]				
4′-OMe			55.7[a]	55.7[a]				
NMe			30.9	31.2			33.2	33.7

Additional NMR data: (J couplings in Hz)

2 J(C-4, H-4) ≈ 179; J(C-4, H-6) 12.1 or 11.3; J(C-6, H-6) ≈ 179; J(C-6, H-4) 11.3 or 12.1; J(C-3a, NMe) 0; J(C-3a, H-4) 7.1; J(C-3a, H-6) 1.6; J(C-3a-H-7) 4.9; J(C-7a, NMe) 3.0; J(C-7a, H-4) 6.0; J(C-7a, H-6) 9.0; J(C-1′, H-3′) 6.0 or 8.1; J(C-1′, H-5′) 8.1 or 6.0; J(C-3′, H-3′) 160.1; J(C-3′, H-5′) 4.9; J(C-6′, H-6′) 162.7.

3 J(C-4, H-4) 181.9; J(C-4, H-6) 12.4; J(C-6, H-6) 177.7; J(C-6, H-4) 11.4; J(C-7, H-7) 164.2; J(C-7, H-6) 7.9; J(C-3a, NMe) present but signal too broad to measure; J(C-7a, NMe) 0; J(C-7a, H-4) 4.3; J(C-7a, H-6) 8.0; J(C-1′, H-3′) 6.2; J(C-1′, H-5′) 6.2; J(C-3′, H-3′) 4.1; J(C-6′, H-6′) 161.9.

[a] Assignments may be reversed.

[b] From Ref. 2 measured in D_2O.

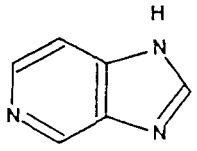
[c] From Ref. 3 measured in D_2O; **6** has shifts reassigned.

previous assignments[1-3] of these carbons in imidazo[4, 5-*c*]pyridines **1**, **4**, **5** and **6**.

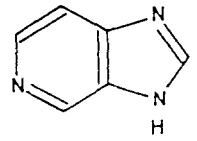
From the ^{13}C shifts in Table 1 for the tautomers **1a** and **1b**, it is clear from a direct comparison with **2** and **3** that **1a** must be the 1-NH tautomer and **1b** is the 3-NH tautomer, making the valid assumption that the substitution of H by Me has a negligible chemical shift effect, as has been shown previously.[4] Consequently, the previous assignments of the tautomers[1] in **1** are confirmed. However, the reported assignments for C-3a and C-7a in compounds **4** and **6**[2,3] have been interchanged from those given originally, and are now as reproduced in Table 1 to give a consistent set for all the compounds.

Having identified the shifts of C-3a and C-7a unambiguously using NMe compounds, it is possible to estimate the proportions of tautomers in compound **4** where only a time-averaged spectrum is observed.

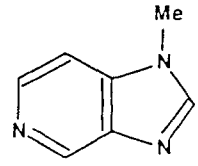
Thus, the observed ^{13}C chemical shifts of **4** are averages of the chemical shifts of its two tautomers **4a** and **4b**, weighted according to their proportions. Since *N*-methylation has little effect on ^{13}C chemical shifts,[4] the ^{13}C chemical shifts of **4** may be treated as weighted averages of the shifts in its NMe analogues **5** and **6**. Calculation using the corrected ^{13}C shifts for C-3a, C-7a and C-6 for **4**, **5** and **6**[3] gives the ratio of tautomers as **4a**:**4b** = 2.3 ± 0.2. (Using the C-7 shift gives almost equal proportions of tautomers).



4a



4b



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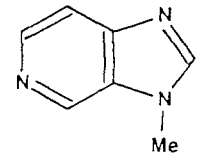

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