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Carbon-13 NMR Studies on Azolopyridines

4†—The Thiazolopyridine Systems

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The ^{13}C NMR spectra of thiazolopyridine systems are discussed. One-bond and long-range $^{13}C–^{1}H$ coupling constants were determined from line splittings and a simple method for distinguishing between 2-methylthiazolo- and 3-methylisothiazolopyridines is suggested. © 1997 by John Wiley & Sons Ltd.

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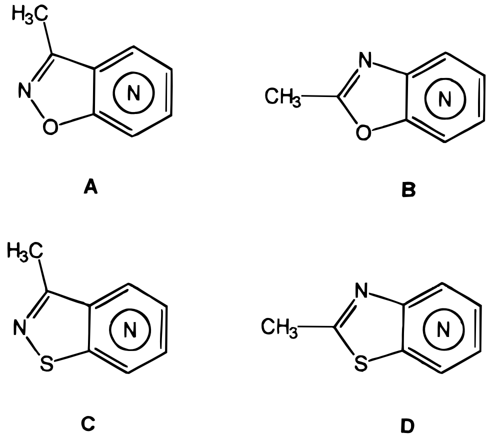
INTRODUCTION

As a continuation of our NMR studies on isoxazolo-[2] (**A**), oxazolo-[3] (**B**) and isothiazolopyridines[1] (**C**) (Scheme 1) and following our interest in azabenzazole chemistry,[4,5] we have now synthesized all four fully aromatic thiazolopyridine isomers (**D**) to examine how the different fused five-membered heterocycle influences the chemical and spectroscopic properties.

We report here the unambiguous assignment of carbon-13 chemical shifts of these systems together with the values of one-bond and long-range $^{13}C–^{1}H$ coupling constants showing that azole ring fusion on the pyridine system is responsible for a significant increase in all one-bond couplings. Moreover, we suggest how ^{13}C NMR spectroscopy can be valuable for distinguishing between the isomeric structures **C** and **D**, their distinction not being easily achievable by other common spectroscopic techniques (MS, IR and ^{1}H NMR).

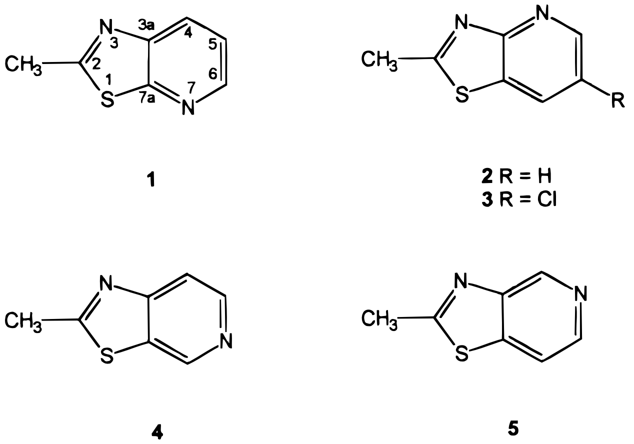


Scheme 1

RESULTS AND DISCUSSION

Chemical shift data for the thiazolopyridines **1–5** (Scheme 2) are given in Table 1. The resonances of the carbon atoms were assigned on the basis of 2D experiments (HETCOR and COLOC), on chemical shift considerations and on the fine splitting pattern present in the coupled spectra. The coupling constants values given in Table 2 were extracted from the gated decoupled spectra which were analysed on a first-order basis, the necessary assumptions being fulfilled.

The resonances of the quaternary carbon atoms C-2, C-3a and C-7a are easily found in the decoupled and DEPT spectra of all the thiazolopyridines considered. In all cases C-2, the assignment of which is confirmed by the quartet from $^{2}J(C\text{-}2, CH_3)$, in the coupled spectra, resonates at highest frequency (168.08–172.64



Scheme 2

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Table 1. ^{13}**C NMR chemical shifts (**δ**, ppm) of thiazolopyridines in CDCl**$_3$

Compound	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a	CH$_3$
1	168.11	146.33	129.22	121.01	146.55	—	159.00	20.93
2	170.59	164.15	—	147.70	119.38	130.15	129.02	20.68
3	171.33	162.47	—	146.88	127.62	129.44	129.90	20.84
4	172.64	158.26	116.85	145.62	—	143.81	132.86	20.35
5	168.08	149.98	144.29	—	143.40	116.21	143.685	20.05

ppm) and this resonance is strictly comparable to the value observed for 2-methyl[*d*]benzothiazole in the same solvent (166.92 ppm).

As regards the C-3a and C-7a carbon atoms, their chemical shifts depend strongly on the position of the pyridine nitrogen atom, the effect of which, as summarized in Table 3, can be deduced by comparison with the chemical shifts of the corresponding atoms of 2-methylbenzo[*d*]thiazole (see Experimental). However, whereas their assignment is straightforward in the thiazolo[4,5-*b*]- and thiazolo[5,4-*c*]pyridine systems (**2** and **4**, respectively), simple chemical shift considerations did not always allow an unambiguous assignment in the other systems and this was achieved only on the basis of the long-range coupling constants and confirmed by COLOC experiments carried out with the required delays. For example, for 2-methylthiazolo[4,5-*c*]pyridine (**5**), the two signals at 149.98 and 143.685 ppm were attributed to C-3a and C-7a, respectively, through the different splitting patterns present in the coupled spectrum [a doublet of doublets from ^{2}J(3a,4) and ^{3}J(3a,7), appearing as a pseudo-triplet, and a doublet of doublets from ^{3}J(7a,6) and ^{3}J(7a,4), respectively]; now, the ^{1}H NMR spectrum of **5** being unambiguously assigned (see Table 4), a COLOC experiment optimized for a 9 Hz coupling showing connectivity between the low-frequency signal and H-6 confirmed the present attribution.

For **1**, the signal at 159.00 ppm [doublet of doublets with ^{3}J(C-7a–N-7–H-6) = 14.0 Hz and ^{3}J(C-7a–C-3a–H-4) = 6.4 Hz] is assigned to C-7a since it is coupled both to H-6 and to the C-4 methine proton, whereas the signal of C-3a (146.33 ppm) is shifted to low-frequency and coupled only to H-5, as confirmed by the COLOC spectrum. For **2**, the two signals at 164.15 and 129.02 ppm were easily attributed to C-3a and C-7a, respectively, on the basis of simple chemical shifts considerations; as well as for the corresponding 2-methyloxazolo[4,5-*b*]pyridine,[3] the assignment was confirmed by the larger value of ^{3}J(C-3a–N-4–H-5) compared with that of ^{3}J(C-7a–C-7–H-6).

Considering the tertiary carbon atoms, their resonances are generally assigned on the basis of the fine splitting pattern or with the help of the HETCOR spectrum. For example, the resonances at 146.55, 129.22 and 121.01 ppm in **1** were assigned to C-6 (α to the nitrogen atom, $^{1}J = 181.1$ Hz), C-4 and C-5, respectively; according to the trend reported previously for pyridines,[6] pyrazolopyrimidines[7] and isoxazolo-,[2] oxazolo-[3] and isothiazolopyridines,[1] the ^{2}J(C-β,H-α) values are larger than any other two-bond coupling constants for the compounds examined (Table 2). In **2**, the unsubstituted carbon atoms C-5, C-6 and C-7 absorb at 147.70, 119.38 and 130.15 ppm, respectively; the assignment of the last two resonances was tentatively achieved on the basis of the different values of geminal (H-α) and vicinal coupling constants [^{2}J(C-6,H-5) = 9.0 Hz *vs.* ^{3}J(C-7,H-5 = 7.2 Hz]. This assignment was then confirmed by a simple HETCOR spectrum, the resonances of H-6 and H-7 being easily identified in the proton spectrum (Table 4).

The three methine ring carbons of **4** were unambiguously assigned on the basis of H–C correlations; thus, the carbon absorbing at 143.81 ppm, being connected to the highest frequency proton, appearing as a small doublet, is assigned to C-7, whereas the resonance at 145.62 ppm must be attributed to C-5. The proton spectrum was used again as the starting point for the identification of the correlated carbon resonances through the HETCOR spectrum for **5**; the attribution of C-4 and C-6 resonances can be unambiguously made by means of the connectivity of the signal at 144.29 ppm with the highest frequency proton at δ 9.172, which on the basis of chemical shift considerations must be attributed to H-4 that appears as a very small doublet [J(4,7) = 0.9 Hz]. Thus, the resonance at 143.40 ppm cross-correlated to the proton at 8.421 ppm [doublet, J(6,7) = 5.4 Hz] belongs to C-6. We wish to point out that this assignment could have been done also by means of the long-range couplings values; in fact, the former signal appears in the coupled spectrum as a doublet of doublets of doublets with $^{1}J = 182.4$ Hz, $J = 11.6$ Hz and $J = 1.3$ Hz, whereas the latter at 143.40 ppm, which is also a doublet of doublets of doublets, shows two analogous couplings ($^{1}J = 181.0$ Hz and $J = 11.7$ Hz) and a third one ($J = 2.2$ Hz) that is too high to be attributed to a four-bond coupling [^{4}J(C-4,H-7)] in this class of compounds.[1–3]

Comparison of ^{1}J(C,H) values (Table 5) for pyridine and oxazolo- and thiazolopyridines shows that the 2-methylthiazole ring fusion is responsible for an increase in all one-bond coupling constants with respect to pyridine, thus confirming the electron-withdrawing effect of the fused five-membered ring. On the other hand, the thiazolopyridines ^{1}J(C,H) values are slightly smaller than those previously reported for oxazolopyridines.[3]

Finally, the chemical shift of the 2-methyl carbon atom deserves some consideration. Apart from the expected high-frequency shift observed for this substituent on going from the previously reported oxazolo- to the thiazolopyridines (δ 14.0–14.6 *vs.* 20.05–20.93 ppm, respectively), it is worth noting that the distinction between thiazolo- and isothiazolopyridine systems can be easily achieved on the basis of the chemical shift of the methyl group, without a detailed analysis of other spectral data. According to the behaviour of 3-

Table 2. Coupling constants, *J*(C,H) (absolute values in Hz), for thiazolopyridines 1–5 in $CDCl_3$

Compound	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a	CH_3
1	$^2J(2,CH_3) = 7.3$	$^3J(3a,5) = 8.8$	$^1J(4,4) = 165.1$ $^3J(4,6) = 7.0$	$^1J(5,5) = 164.2$ $^2J(5,6) = 9.0$	$^1J(6,6) = 181.1$ $^2J(6,5) = 3.7$ $^3J(6,4) = 7.2$	—	$^3J(7a,6) = 14.0$ $^3J(7a,4) = 6.4$	$^1J = 130.2$
2	$^2J(2,CH_3) = 7.4$	$^3J(3a,5) = 13.1$ $^3J(3a,7) = 5.8$	—	$^1J(5,5) = 180.0$ $^2J(5,6) = 3.7$ $^3J(5,7) = 7.2$	$^1J(6,6) = 165.0$ $^2J(6,5) = 9.0$	$^1J(7,7) = 166.8$ $^2J(7,6) = 1.5$ $^3J(7,5) = 7.2$	$^2J(7a,6) = 8.9$	$^1J = 130.4$
3	$^2J(2,CH_3) = 7.4$	$^3J(3a,5) = 12.6$ $^3J(3a,7) = 6.0$	—	$^1J(5,5) = 187.5$ $^3J(5,7) = 4.8$	$^2J(6,5) = 4.5$ $^2J(6,7) = 4.5$	$^1J(7,7) = 171.5$ $^3J(7,5) = 5.3$	Multiplet	$^1J = 130.6$
4	$^2J(2,CH_3) = 7.3$	Multiplet	$^1J(4,4) = 166.0$ $^2J(4,5) = 8.3$ $^4J(4,7) = 2.0$	$^1J(5,5) = 180.2$ $^2J(5,4) = 2.4$ $^3J(5,7) = 11.7$	—	$^1J(7,7) = 184.6$ $^3J(7,5) = 12.2$ $^4J(7,4) = 1.0$	Multiplet	$^1J = 130.4$
5	$^2J(2,CH_3) = 7.4$	$^2J(3a,4) = 6.2$ $^3J(3a,7) = 6.2$	$^1J(4,4) = 182.4$ $^3J(4,6) = 11.6$ $^4J(4,7) = 1.3$	—	$^1J(6,6) = 181.0$ $^2J(6,7) = 2.2$ $^3J(6,4) = 11.7$	$^1J(7,7) = 167.8$ $^2J(7,6) = 9.5$ $^4J(7,4) = 1.7$	$^3J(7a,6) = 9.1$ $^3J(7a,4) = 6.0$	$^1J = 130.4$

Table 3. Effect of the pyridine nitrogen atom on the C-3a and C-7a absorption of thiazolopyridines (ppm)

Compound	ΔC3-a[a]	ΔC7-a
1	−7.04	+23.37
2	+10.78	−6.61
4	+4.89	−2.77
5	−3.39	+8.055

[a] ΔC = δC(thiazolopyridines − δC (for the corresponding carbon in 2-methylbenzo[*d*]thiazole in $CDCl_3$; see Experimental).

methylbenzo[*d*]isothiazole[1] and 2-methylbenzo[*d*]thiazole ($\delta_{CH_3} = 17.39$ *vs.* 20.11 ppm), this substituent exhibits, on going from isothiazolo- to thiazolopyridine systems, a diagnostic high-frequency shift (δ 16.82–17.99 *vs.* 20.05–20.93 ppm, respectively), thus easily allowing the distinction between systems of type **C** or **D** (Scheme 1).

EXPERIMENTAL

Compounds

Thiazolopyridines **1**,[8] **4**[9] and **5**[9] were synthesized according to the published procedures. 2-Methylbenzo[*d*]thiazole is commercially available (Aldrich): ^{13}C NMR ($CDCl_3$), 20.11 (2- CH_3), 121.37 (C-5/C-6), 122.37 (C-6/C-5), 124.67 (C-4/C-7), 125.89 (C-7/C-4), 135.63 (C-7a), 153.37 (C-3a), 166.92 (C-2).

Compound **3** was prepared by an extension of the method of Couture *et al.*:[9] reaction of the commercial 2-amino-3,5-dichloropyridine with ethyl ethanethioate[10] in the presence of LiH afforded 6-chloro-2-methylthiazolo[4,5-*b*]pyridine (**3**). Treatment of this compound with H_2 on Pd/C gave the thiazolopyridine **2**.

Compound 3. M.p. 137–138 °C after sublimation at 105 °C/0.5 mmHg (found, C 45.7, H 2.9 N 15.0; $C_7H_5N_2SCl$ requires C 45.5, H 2.7, N 15.2%); IR (KBr), $\nu = 3087$, 3027, 1512, 1368 and 1167 cm^{-1}; mass spectrum, *m*/*z* (relative intensity, %), 186 ($M^+ + 2$, 37), 184 (M^+, 85), 108(100).

Compound 2. M.p. 68–69 °C from light petroleum (lit.[11] b.p. 100–100.5 °C/10 mmHg) (found, C 56.1, H 4.1, N 18.5; $C_7H_6N_2S$ requires C 56.0, H 4.0, N 18.65%); IR (KBr), $\nu = 3090$, 3050, 1569 and 1386 cm^{-1}; mass spectrum, *m*/*z* (relative intensity, %), 150 (M^+, 100), 109(54), 82(29).

Spectra

All NMR spectra were obtained on a Varian VXR-300 instrument operating in the PFT mode at 300 MHz for ^1H and 75.43 MHz for ^{13}C with spectra recorded for solutions 0.1 M in $CDCl_3$ on a switchable $^1H/^{13}C$ 5 mm probe (^{13}C 90° pulse width = 15 μs, ^1H 90° pulse width = 16 μs). Multiplicities were determined using the DEPT technique and proton coupled spectra were obtained in the 'gated decoupling' mode. One-dimensional ^1H and ^{13}C spectra were recorded for 3000 and 14 500 Hz spectral windows, respectively, using 32K data points (zero-filled to 64K) corresponding to 0.09 Hz per point ^1H digital resolution and 0.44 Hz per

Table 4. ^1H NMR data (δ, ppm) of thiazolopyridines in $CDCl_3$[a]

Compound	H-4	H-5	H-6	H-7	CH_3
1	8.122 dd *J*(4,5) = 8.2 *J*(4,6) = 1.6	7.349 dd *J*(5,4) = 8.2 *J*(5,6) = 4.6	8.488 dd *J*(6,5) = 4.6 *J*(6,4) = 1.6	—	2.816 s
2	—	5.591 dd *J*(5,6) = 4.7 *J*(5,7) = 1.6	7.187 dd *J*(6,7) = 8.0 *J*(6,5) = 4.7	8.090 dd *J*(7,6) = 8.0 *J*(7,5) = 1.6	2.807 s
3	—	8.550 d *J*(5,7) = 2.0	—	8.095 d *J*(7,5) = 2.0	2.840 s
4	7.801 dd *J*(4,5) = 5.7 *J*(4,7) = 1.0	8.581 d *J*(5,4) = 5.7	—	9.03 d *J*(7,4) = 1.0	2.869 s
5	9.172 d *J*(4,7) = 0.9	—	8.421 d *J*(6,7) = 5.4	7.711 dd *J*(7,6) = 5.4 *J*(7,4) = 0.9	2.806 s

[a] s = singlet, d = doublet, dd = doublet of doublets.

Table 5. One-bond C,H coupling constants of thiazolopyridines in $CDCl_3$ (Hz) and differences (Δ_A and Δ_B) in ^1J(C,H) relative to the corresponding carbon atom in unsubstituted pyridine and oxazolopyridines,[a] respectively

Compound	C-4	Δ_A	Δ_B	C-5	Δ_A	Δ_B	C-6	Δ_A	Δ_B	C-7	Δ_A	Δ_B
1	165.1	(+2.1)	(−2.0)	164.2	(+2.2)	(−0.9)	181.1	(+4.1)	(−1.7)	—	—	—
2	—	—	—	180.0	(+3.0)	(0)	165.0	(+3.0)	(−0.3)	166.8	(+3.8)	(−2.2)
4	166.0	(+4.0)	(−2.7)	180.2	(+3.2)	(−0.6)	—	—	—	184.6	(+7.6)	(−1.4)
5	182.4	(+5.4)	(−0.9)	—	—	—	181.0	(+4.0)	(−1.9)	167.8	(+5.8)	(−0.3)

[a] For the one-bond coupling constants of pyridine and oxazolopyridines, see Refs 6 and 3, respectively.

point ^{13}C digital resolution. Chemical shifts are relative to internal TMS.

The 2D NMR spectra were recorded using the standard Varian software and the sample temperature was controlled at 295 K for all spectra. For the HETCOR and COLOC experiments the ^{1}H spectral width was 2100 Hz and the ^{13}C spectral width 9640 Hz. The HETCOR experiments were set up for $^{1}J = 170$ Hz and 128 transients were accumulated into 2048 real points for each of the 256 increments in t_1. The COLOC experiments were set up for $^{1}J = 170$ Hz and $^{n}J(C,H) = 6$ or 9 Hz, and 128 transients were accumulated into 2048 real points for each of the 128 increments in t_1. The mass spectra were recorded on a Carlo Erba QMD 1000 instrument operating in the EI mode, with ionizing potential 70 eV and source temperature 250 °C.

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