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Nitroimidazoles: Part X—Spectral Studies on Isomeric 1-Substituted 4- & 5-Nitroimidazoles & Some 2-Nitroimidazoles* †‡

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Nitroimidazoles: Part X—Spectral Studies on Isomeric 1-Substituted 4- & 5-Nitroimidazoles & Some 2-Nitroimidazoles* †‡

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Chemical shifts of C-4 in series-a of 1-substituted 5-nitroimidazoles fall within a narrow range of 130-133 ppm and those of C-5 in isomeric 4-nitro compounds (series-b) at 120-124 ppm, offering a method for distinguishing between isomeric pairs. An additional diagnostic method utilises the observation that for series-b, the signal due to C-5 has extra multiplicity due to three-bond coupling with protons of the group on N-1, which C-4 in series-a does not exhibit. DMSO induced chemical shifts for C-5 H in series-b (δ DMSO-$d_6 - \delta$ $CDCl_3$) are much larger than those for C-4H in series-a and are useful aids for structure assignment. Mass spectra of the 1-alkyl-5-nitroimidazoles (series-a) generally show fragments due to loss of OH, which are mostly absent in series-b; the loss of NO_2 is also more intense in the former than in the latter. The phenomena are traced to participation by the alkyl group at position-1. Acid and alkali induced shifts in water and EtOH UV spectra of a variety of nitroimidazoles are described and discussed. 1-Alkyl-5-nitroimidazoles undergo hypsochromic shifts in 0.1*N* H_2SO_4 more readily than the 4-nitro-isomers. On silica gel plates, compounds of series-a generally move faster than those of series-b. The melting points of the 5-nitroimidazoles are as a rule lower than those of the 4-nitro counterparts.

Our extensive studies on nitroimidazoles which culminated in the clinical development of 1-methyl sulphonyl-3-(1-methyl-5-nitroimida zol-2-yl)-2-imida-zolidinone[1] (Code No. C10213-GO) led to the examination of a large number of isomeric 1-methyl-4- and 5-nitroimidazoles carrying diverse substituents in the rest of the molecule and to the confirmation of literature reports that the 5-nitroimidazole derivatives as a rule have greater antiprotozoal activity than their 4-nitro counterparts.

The general synthetic procedures for these compounds involve either the introduction of a nitro group by electrophilic substitution of imidazoles or alkylation (arylation) of nitroimidazoles unsubstituted on the nitrogen atoms. Some procedures are also available wherein 1-substituted-4- or 5-nitroimida-zoles carry other atoms or groups which allow further manipulations. While the last route permits structural identification, the two others mentioned earlier, viz. nitration or alkylation can lead to either one or a mixture of two isomers necessitating correct structural assignments[2-4]. The significance of the location of the nitro group B for antiprotozoic activity requires unambiguous methods for structure identification. Various spectral (UV[5], NMR[6,7], IR[8]) and other physical properties (pK_a)[5] have been used for this purpose in the past with limited success. We wish to report in this paper the efficacies of using ^{13}C NMR spectral data, solvent-induced ^1H NMR shifts and mass and UV spectral characteristics for this purpose. Differences in TLC behaviour and m.p.s are also noted. The study revealed that of all these techniques ^{13}C NMR shifts and coupling pattern and to a lesser extent solvent-induced proton shifts could provide satisfactory structural solutions even when only one isomer was available. We also include in this paper studies of a few 2-nitroimidazole derivatives.

^{13}C NMR Studies

The spectra were run in $CDCl_3$, DMSO-d_6 or a mixture of the two solvents; chemical shifts are expressed in δ-scale (ppm) downfield from TMS as reference. In one case, the spectra were taken in the first two solvents; since there were no significant differences in the chemical shifts solvent-dependent phenomena were considered unlikely (in contrast to protons, *vide infra*) to vitiate the studies and conclusions.

There are a few reports in the literature[9,9a,10] dealing with some imidazole shifts and coupling constants. Of particular interest is the observation that the one-bond C—H coupling of C-2 (208 Hz) in imidazole is significantly larger than that of C-4 and C-5 (190 Hz)[10]. This has been used advantageously to revise the structure of the so-called 2,4-diiodo-imidazole[11] and 2-iodo-4-nitroimidazole[5] respectively to 4,5-diiodoimidazole and 4-iodo-5-nitroimida-zole[4,12]. ^{13}C and ^{15}N shifts have been reported for 4-nitroimidazole and its 1- and 2-methyl derivatives[9a].

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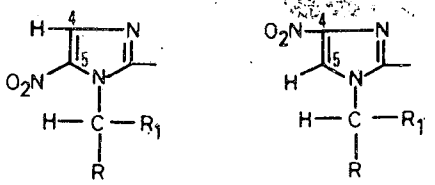


a b

R = R_1 = H or other groups

We have successfully used three-bond carbon-hydrogen coupling for structure assignments of addition products of dinucleophiles to acetylene-dicarboxylic esters[13], pyrazoles from unsummetrical 1,3-diketones[14] and isomeric nitropyrazoles[15]. This led us to believe that in the first instance, the isomeric structures (**a**) and (**b**) would be readily distinguishable by scrutiny of the multiplicity of the signal due to C-4 and C-5. The former carbon atom in (**a**) would exhibit a large one-bond coupling (~200 Hz) with the proton on it while C-5 would have a two-bond coupling with C-4 H (10-12 Hz) and a three-bond coupling with the protons on the group at position-1 (~3 Hz). On the other hand, the signal due to C-4 in (**b**) would be a doublet due to two-bond coupling with C-5H (~6 Hz) while C-5 would manifest a large one-bond coupling with C-5H (~200 Hz) and further small three-bond couplings with the protons on the group at position-1.

In the light of these assumptions several pairs were studied and the data are presented in Table 1. The ensuing discussion is restricted to imidazole C-atoms. Other ^{13}C data are for information and documentation. It became immediately apparent that while the signal due to C-4 in (**a**) could be identified readily, that C-5 being quaternary was sometimes not discernible and very often not unambiguously assigned. Likewise, C-5 in (**b**) was located with certainty but the quaternary C-4 atom posed difficulties and was often not easily distinguished from the signal due to C-2, when the latter carried a substituent which was the case in most of the compounds (Extensive single resonance proton decoupling studies might have helped but were not undertaken). In the case of a few compounds, viz. **3**, **4**, **5**, **6**, **8**, **12**, **36** with an unsubstituted C-2, there was a need to distinguish it from C-4 in (**a**) or C-5 in (**b**). This was done readily on the basis of one-bond coupling constants. These values were respectively for C-2 and C-4 (C-5) in various imidazoles as follows: imidazoles carrying no electronegative substituents—205-210, 186-190; chloroimidazoles, 210, 192-194; nitroimidazoles, 212-222, 200-208 Hz. **36b** with two NO_2 groups is unique in having $^1J_{C(2)H(2)} = 233$ Hz and $^1J_{C(5)H(5)} = 213$ Hz. The increase in the value of $^1J_{CH}$ due to an adjacent electron-withdrawing group is known[16]. The signal due to C-2 exhibited further multiplicity as

Table 1—^{13}C NMR Data for Nitroimidazoles*

Compd	C-2			C-4			C-5			Others**			
	δ	J		δ	J		δ	J		δ		J	
1	135.4	C(2)H(2) C(2)H(4)	204.4 8.8	121.9	C(4)H(4) C(4)H(5) C(4)H(2)	188.2 13.3 7.4	—	—		—		—	
2	144.8	C(2)H(4) C(2)H(CH_3)	7.4 7.4	121.3	C(4)H(4) C(4)H(5)	188.2 11.7	—	—		CH_3	13.7	$^1J_{CH}$	128.0
3	138.6	C(2)H(2)	210.3†	129.2	C(4)H(4) C(4)H(5) C(4)H(2)	186.8 10.3 10.3	121.0	C(5)H(5) C(5)H(4) C(5)H(2) C(5)H(CH_3)	185.3 16.2 3.0 3.0	CH_3	32.9	$^1J_{CH}$	139.8
4	144.9	††		126.4	C(4)H(4) C(4)H(5)	186.7 10.3	120.9	C(5)H(5) C(5)H(4) C(5)H(CH_3)	186.7 16.2 2.9	NCH_3 CCH_3	32.2 12.3	$^1J_{CH}$ $^1J_{CH}$	138.0 128.0
5	136.9	C(2)H(2)	208.0†	130.2	C(4)H(4) C(4)H(5) C(4)H(2) C(4)H(2)	188.8 11.4 9.9	116.5	C(5)H(5) C(5)H(4) C(5)H(2) C(5)N−C*H*	190.7 16.5 3.3 3.3	NCH= $=CH_2$	130.2 101.1	$^1J_{CH}$ $^1J_{CH}$ $^2J_{CH}$	177.4 160.8 3.6
6a	137.3	C(2)H(2) C(2)H(4) C(2)H(CH_3)	210.3 10.3 2.9	125.6	C(4)H(4) C(4)H(2)	194.1 8.8	118.2	††		$N-CH_3$	30.0	$^1J_{CH}$	141.2
6b	137.7	C(2)H(2) C(2)H(5) C(2)H(CH_3)	210.3 3.0 3.0	129.0	C(4)H(5) C(4)H(2)	15.0 7.0	117.3	C(5)H(5) C(5)H(2) C(5)H(CH_3)	192.7 3.0 3.0	$N-CH_3$	34.3	$^1J_{CH}$	141.2
7	135.6	C(2)H(2) C(2)H(5)	214.0 9.0	147.1	††		118.6	C(5)H(5) C(5)H(2)	200.1 3.0				

(Contd)

Table 1—^{13}C NMR Data for Nitroimidazoles* — (*Contd*)

Compd.	C-2		C-4		C-5		Others**	
	δ	J	δ	J	δ	J	δ	J
8a	141.3	C(2)H(2) 213.0 C(2)H(4) 11.8 C(2)H(CH_3) 4.4	132.1	C(4)H(4) 200.1 C(4)H(2) 10.3		—	N−CH_3 34.3	$^1J_{CH}$ 143.6
8b	136.0	C(2)H(2) 210.8 C(2)H(5) 8.9 C(2)H(CH_3) 4.5	— — —	— — —	120.1 — —	C(5)H(5) 200.0 C(5)H(2) 3.0 C(5)H(CH_3) 3.0	N−CH_3 33.3	$^1J_{CH}$ 141.3
9	145.3	C(2)H(5) 9.0 C(2)H(CH_3) 7.0	147.0	C(4)H(5) 6.2	119.1	C(5)H(5) 200.0	C−CH_3 13.8	$^1J_{CH}$ 129.6
10a	134.0 (?)	—	131.7	C(4)H(4) 198.6	142.9 (?)	††	N−CH_3 32.7 C−CH_3 13.5	$^1J_{CH}$ 143.2 $^1J_{CH}$ 129.4
10b	145.0	††	145.0 (?)	—	122.3	C(5)H(5) 200.5 C(5)H(CH_3) 3.0	N−CH_3 32.2 C−CH_3 12.1	$^1J_{CH}$ 141.5 $^1J_{CH}$ 129.5
11a	139.4 (?)	††	132.4	C(4)H(4) 200.2	150.7 (?)	*d*(?)	C−CH_3 14.2 ArC(1) 140.6 ArC(2), C(6) 129.0 ArC(3), C(5) 124.8 ArC(4) 148.3	$^1J_{CH}$ 130.2 *t*** $^1J_{CH}$ 170.9 $^2J_{CH}$ 5.8 $^1J_{CH}$ 172.8 $^2J_{CH}$ 5.4 *t***
11b	147.9	††	146.9	*d*(?)	121.5	C(5)H(5) 204.1≈	C−CH_3 13.8 ArC(1) 141.0 ArC(2), C(6) 127.0 ArC(3), C(5) 125.1 ArC(4) 144.7	$^1J_{CH}$ 130.2 *t*** $^1J_{CH}$ 169.9 $^2J_{CH}$ 4.8 $^1J_{CH}$ 171.9 $^2J_{CH}$ 4.8 *t***
12a	142.1	C(2)H(2) 215.0 C(2)H(4) 10.0 C(2)H(CH_2) 4.0	133.2	C(4)H(4) 199.9 C(4)H(2) 10.0	134.1	††	Not analysed	
12b	136.7	C(2)H(2) 216.0 C(2)H(5) 8.5 C(2)H(CH_2) 3.5	142.9	††	120.4	C(5)H(5) 201.0 C(5)H(2) 3.5 C(5)H(CH_2) 3.5	Not analysed	
13a	151.9	††	132.9	C(4)H(4) 199.0	138.5	C(5)H(4) 12.0 C(5)H(CH_2) 4.0	CH_2OH 54.9 N−CH_2 48.3 C−CH_3 14.2	*t*** *t*** *q***
13b	145.1	††	145.1	C(4)H(5) 6.0	121.8	C(5)H(5) 200.0 C(5)H(CH_2) 4.0	CH_2OH 60.0 N−CH_2 49.1 C−CH_3 12.4	$^1J_{CH}$ 142.0 $^1J_{CH}$ 140.0 $^1J_{CH}$ 130.0
14a	152.1	††	132.9	C(4)H(4) 198.5	138.9	C(5)H(4) 11.0 C(5)H(CH_2) 3.5	CHOH 65.9 N−CH_2 52.8 CH−CH_3 20.9 2-CH_3 14.4	*d*** *t*** *q*** *q***
14b	145.4 (?)	††	145.4	C(4)H(5) 6.0	122.3	C(5)H(5) 200.4 C(5)H(CH_2) 3.8	CHOH 65.4 N−CH_2 53.4 $CHCH_3$ 20.5 2-CH_3 12.7	$^1J_{CH}$ 144.1 $^1J_{CH}$ 139.3 $^1J_{CH}$ 125.8 $^1J_{CH}$ 129.4
15a	152.1	††	132.3	C(4)H(4) 200.2	138.5	C(5)H(4) 11.8 C(5)H(CH_2)††	CHOH 69.9 N−CH_2 49.8 CH_2Cl 47.0 C−CH_3 14.4	$^1J_{CH}$ 150.0 $^1J_{CH}$ 143.5 $^1J_{CH}$ 150.8 $^1J_{CH}$ 129.8
15b	145.6 (?)	††	145.6 (?)	C(4)H(5) 6.5 (?)	122.4	C(5)H(5) 200.9 C(5)H(CH_2) 3.5	CHOH 69.4 N−CH_2 49.8 CH_2Cl 46.7 C−CH_3 12.7	$^1J_{CH}$ 150.0 $^1J_{CH}$ 140.0 $^1J_{CH}$ 150.0 $^1J_{CH}$ 130.0

(*Contd.*)

Table 1—^{13}C NMR Data for Nitroimidazoles* —(*Contd*)

Compd.	C-2		C-4		C-5		Others**		
	δ	J	δ	J	δ	J	δ		J
16a	151.5	††	133.1	C(4)H(4) 199.0	138.5	C(5)H(4) 11.0 C(5)H(CH_2) 4.0	NCH_2CH_2 $SO_2CH_2CH_3$ $N-CH_2$ 2-CH_3 CH_2-CH_3	49.8 47.1 39.1 13.9 5.9	*t*** *t*** *t*** *q*** *q***
16b	145.3	††	145.4	C(4)H(5) 5.4	122.1	C(5)H(5) 201.2 C(5)H(CH_2) 3.4	NCH_2CH_2 CH_2CH_3 $N-CH_2$ 2-CH_3 CH_2CH_3	50.0 47.1 39.6 12.5 5.8	*t*** *t*** *t*** *q*** *q***
17	146.1	††	130.9	C(4)H(5) 12.3	120.8	C(5)H(5) 203.6	—		—
18a	?	—	131.6	C(4)H(4) 203.6	?	—	$N-CH_3$	34.4	$^1J_{CH}$ 144.6
18b	144.1 (?)	—	131.5 (?)	—	123.5	C(5)H(5) 207.5 C(5)H(CH_3) 2.8	$N-CH_3$	34.0	$^1J_{CH}$ 143.5
19	152.0	††	124.7	C(4)H(4) 190.0 C(4)H(5) 9.0	118.5	C(5)H(5) 192.0 C(5)H(4) 15.0 C(5)H(CH_3) 3.0	$O-CH_2$ $N-CH_2$ $N-CH_3$	66.5 51.1 31.7	$^1J_{CH}$ 145.0 $^1J_{CH}$ 145.0 $^1J_{CH}$ 139.7
20a	155.4	††	132.1	C(4)H(4) 198.6	?	?	$O-CH_2$ $N-CH_2$ $N-CH_3$	65.5 49.4 33.8	$^1J_{CH}$ 144.1 $^1J_{CH}$ 139.0 $^1J_{CH}$ 142.7
21a	137.9	C(2)H(4) 10.5†	131.0	C(4)H(4) 202.1	143.0	C(5)H(4) 15.0 C(5)H(CH_3) 4.0	C=O $CH_2NSO_2CH_3$ CH_2NCO SO_2CH_3 $N-CH_3$	152.2 43.1 42.1 39.5 34.5	*m*** $^1J_{CH}$ 146.0 $^1J_{CH}$ 152.0 $^1J_{CH}$ 140.7 $^1J_{CH}$ 143.0
21b	?	—	?	—	121.7	C(5)H(5) 202.0 C(5)H(CH_3) 3.0	C=O $CH_2NSO_2CH_3$ CH_2NCO SO_2CH_3 $N-CH_3$	? 43.6 42.1 40.1 34.4	— *t*** *t*** *q*** *q***
26	?	—	128.3	?	128.3	?	—		—
27	145.4	††	127.6	C(4)H(4) 195.3 C(4)H(5) 10.3	128.2	C(5)H(5) 196.1 C(5)H(4) 18.0 C(5)H(CH_3) 3.0	$N-CH_3$	37.2	$^1J_{CH}$ 144.1
28	145.0	††	127.1	C(4)H(4) 195.8 C(4)H(5) 9.5	128.0	C(5)H(5) 200.0 C(5)H(4) 15.0 C(5)H(CH_2) 3.5	CHOH $N-CH_2$ CH_2Cl	68.7 52.0 46.5	$^1J_{CH}$ 148.0 $^1J_{CH}$ 141.0 $^1J_{CH}$ 152.0
29	155.7	C(2)H(5) 15.6	134.9	C(4)H(5) 14.0 C(4)H(CH_2) 4.0	130.7	C(5)H(5) 184.0 C(5)H(CH_2) 3.0	$N-CH_2$ (ring) $C-CH_2$ CH_2CH_2	52.6 51.6 22.8	$^1J_{CH}$ 144.6 $^1J_{CH}$ 145.0 $^1J_{CH}$ 135.7
30a	?	—	129.2	C(4)H(4) 208.0	?	—	$N-CH_3$	36.3	$^1J_{CH}$ 146.1
30b	142.0	††	142.5	††	126.5	C(5)H(5) 206.4 C(5)H(CH_3) 3.7	$N-CH_3$	38.4	$^1J_{CH}$ 145.6
32	142.4	††	128.7	C(4)H(4) 191.0 C(4)H(5) 10.3	122.3	C(5)H(5) 191.0 C(5)H(4) 16.2 C(5)H(CH_3) 3.0	$N-CH_3$ $S-CH_3$	32.7 16.1	$^1J_{CH}$ 139.7 $^1J_{CH}$ 141.2
34a	151.0 (?)	††	133.2	C(4)H(4) 201.4	140.0 (?)	††	$N-CH_3$ $S-CH_3$	33.6 14.4	$^1J_{CH}$ 143.6 $^1J_{CH}$ 143.6
34b	145.0	††	146.8 (?)	—	123.6	C(5)H(5) 200.0 C(5)H(CH_3) 3.0	$N-CH_3$ $S-CH_3$	33.7 15.2	$^1J_{CH}$ 142.3 $^1J_{CH}$ 142.7
35a	146.8	††	130.4	C(4)H(4) 205.1	139.6	††	SO_2CH_3 $N-CH_3$	42.4 34.9	$^1J_{CH}$ 140.6 $^1J_{CH}$ 145.8

(*Contd.*)

Table 1—^{13}C NMR Data for Nitroimidazoles* —(*Contd*)

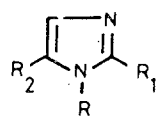
Compd	C-2		C-4		C-5		Others**	
	δ	J	δ	J	δ	J	δ	J
35b	141.8	C(2)H(5) 10.0 C(2)H(CH_3) 4.0	144.9	C(4)H(5) 6.0	126.5	C(5)H(5) 205.0 C(5)H(CH_3) 3.7	SO_2CH_3 43.3 N−CH_3 36.3	$^1J_{CH}$ 140.2 $^1J_{CH}$ 144.1
36b	132.3	C(2)H(2) 233.2 C(2)H(5) 5.8	144.4	C(4)H(2) 16.0†	115.4	C(5)H(5) 213.3 C(5)H(2) 1.5	—	—
37a	148.0	††	134.6	C(4)H(4) 200.2	126.7	C(5)H(4) 16.0	C=O 159.2 OCH_2 61.9 N−CH_3 35.4 C−CH_3 14.2	$^3J_{CH}$ 3.0 $^1J_{CH}$ 145.0 $^1J_{CH}$ 145.5 $^1J_{CH}$ 127.0
38	144.5	††	137.4	††	132.3	††	OCH_2 66.6 C−CH_2 55.0 N−CH_2 53.5 C−CH_2 51.0 N−CH_3 34.0	$^1J_{CH}$ 142.6 $^1J_{CH}$ 135.0 $^1J_{CH}$ 134.0 $^1J_{CH}$ 135.0 $^1J_{CH}$ 143.0
39a	138.9	C(2)H(2) 211.9 C(2)H(CH_3) 3.8	133.2	C(4)H(2) 12.0	?	?	N−CH_3 36.8	*q***
39b	136.5	C(2)H(2) 221.6 C(2)H(CH_3) 3.7	?	—	?	—	N−CH_3 32.8	*q***
40a	143.7	C(2)H(2) 216.7 C(2)H(CH_3) 4.3	90.8	C(4)H(2) 11.8	138.8 (?)	††	N−CH_3 36.2	$^1J_{CH}$ 144.2
40b	139.8	C(2)H(2) 218.6 C(2)H(CH_3) 3.5	149.1	††	81.5	C(5)H(2) 3.0 C(5)H(CH_3) 3.0	N−CH_3 36.2	$^1J_{CH}$ 142.5
42	149.6	††	133.7	C(4)H(4) 189.4 C(4)H(5) 10.2	116.8	C(5)H(5) 191.2 C(5)H(4) 14.9	N−CH_2 45.9 S−CH_2 34.9	$^1J_{CH}$ 146.7 $^1J_{CH}$ 146.7
43	156.5	C(2)H(4) 14.7 C(2)H(CH_2) 3.0	136.8	C(4)H(4) 200.0	138.9	††	N−CH_2 48.3 S−CH_2 35.5	$^1J_{CH}$ 150.0 $^1J_{CH}$ 151.0
45	?	—	137.9	C(4)H(4) 198.3	(?)	—	N−CH_2 54.7 N−CH_2 44.3 N−CH_3 32.4	$^1J_{CH}$ 150.0 $^1J_{CH}$ 150.0 $^1J_{CH}$ 138.4
46	145.6	††	122.7	C(4)H(4) 211.2 C(4)H(CH_3N) 1.8	?	—	?	—

*^{13}C NMR spectra were run in $CDCl_3$ or DMSO-d_6 alone or in a mixture of the two solvents at 22.63 mHz in a Bruker FT NMR spectrometer; δ in ppm and J in Hz.
**Only gross multiplicity is reported and/or analysed; further details not given.
†Further multiplicity not analysed.
††Unanalysed multiplet.
?Signal not located or assignment uncertain.

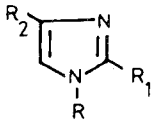
expected if the group at position-1 carried protons. In this case, this multiplicity was seen in both the isomers (**a**) and (**b**).

From the data recorded in Table 1, it became easily possible to identify the 5-nitro isomer (**a**), by the presence of a signal (C-4) in the aromatic region, exhibiting only a *single* one-bond proton coupling of about 200 Hz, while (**b**) was characterised by a signal (C-5) in the same region, appearing as a doublet ($^1J_{CH}$ ~200 Hz) with further substructure due to three-bond couplings—doublet, triplet or quartet, depending upon the number of protons on the group carried by N-1. This was found to be true for *all* the pairs of nitroimidazoles (series a and b) studied: **8**, **10**, **12-16**, **18**, **21**, **30**, **34** and **35**, as also for the chloroimidazoles (**6**). Compounds **6a**, **8a** and **12a** having no substituent at C-2 showed additional three-bond coupling for C-4 with C-2H and **6b**, **8b** and **12b**, a similar coupling of C-5 with C-2H.

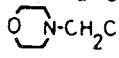
While this approach depending upon the presence or absence of a $^3J_{CH}$ was useful for 4- and 5-nitroimidazoles with a proton-bearing substituent on N-1, it was obvious that this would be invalid if there was no such proton, e.g. **11** and **36**. We believe that differentiation is still possible on the basis of chemical shifts of C-4 in the series-a and C-5 in series-b. It is recalled at this stage that the signals due to these carbon atoms are easily picked up since they bear protons—both by virtue of enhanced intensity due to an NOE in the broad-band decoupled spectrum and to



(a)

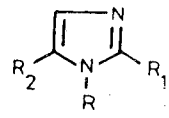


(b)

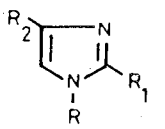
Compd. No.	R	R_1	R_2
1	H	H	H
2	H	Me	H
3	Me	H	H
4	Me	Me	H
5	CH_2=CH-	H	H
6	Me	H	Cl
7	H	H	NO_2
8	Me	H	NO_2
9	H	Me	NO_2
10	Me	Me	NO_2
11	4-$NO_2C_6H_4$	Me	NO_2
12		H	NO_2
13	$HOCH_2CH_2$-	Me	NO_2
14	$MeCH(OH)CH_2$-	Me	NO_2
15	$ClCH_2CH(OH)CH_2$-	Me	NO_2
16	$MeCH_2SO_2CH_2CH_2$-	Me	NO_2
17	H	Cl	NO_2
18	Me	Cl	NO_2
19	Me		H
20	Me		NO_2

a large $^1J_{CH}$ in the gated spectrum. The chemical shifts of C-4 in the nitroimidazoles of series-a fall within the narrow range of 130-133 ppm, with the exception of 1-methyl-2,5-dinitroimidazole (**30a**), which has δ C-4 at 129.2 ppm, while in series-b, δ C-5 falls in the range of 120-124 ppm. In the latter group, **30b**, **35b** and **36b** (δ 126.5, 126.5 and 115.4 ppm respectively) are exceptions. In the case of **11a**, **b**, assignment based upon $^3J_{CH}$ is not possible but the presence of a doublet at 132.4 (C-4) with $^1J_{CH}$ = 200.2 Hz and at 121.5 with $^1J_{CH}$ = 204.1 Hz would be consistent with structures **11a** and **11b** respectively. It is also in accordance with the fact that **11b** was synthesised by treatment of the sodium salt of **9** with *p*-nitrofluorobenzene, while **11a** arose from the nitration of 1-phenyl-2-methylimidazole (but along with **11b**) and also with solvent-induced shifts in the proton spectra of **11a** and **11b** (*vide infra*). Structure **36b**, the nitration product of 4-nitroimidazole[17], with δ C-5 of 115.4 ($^1J_{C(2)H(2)}$ = 233.2 Hz and $^1J_{C(5)H(5)}$ = 213.3 Hz) stands vindicated.

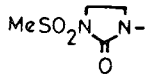
Nothing that in 1-methylimidazole (**3**), C-4 and C-5 have chemical shifts of 129.2 and 121.0 respectively



(a)



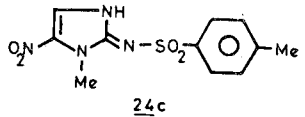
(b)

Compd No.	R	R_1	R_2
21	Me		NO_2
22	Me	$Cl_2CHCONH$	NO_2
23	Me	4-ClC_6H_4CONH	NO_2
24	Me	Tos NH	NO_2
25	Me	Tos -N(Me)-	NO_2
26	H	NO_2	H
27	Me	NO_2	H
28	$ClCH_2CH(OH)CH_2$-	NO_2	H
29	H	NO_2	CH_2N
30	Me	NO_2	NO_2
31	Me	OMe	NO_2
32	Me	SMe	H
33	Me	SO_2Me	H
34	Me	SMe	NO_2
35	Me	SO_2Me	NO_2
36	NO_2	H	NO_2
37	Me	NO_2	CO_2Et

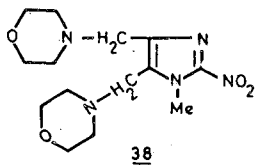
which are not very different from those observed for C-4 in series-a and C-5 in series-b, it becomes obvious that this demarcation is to be mainly attributed to the nature of the nitrogen atom to which they are attached; C-4 to N=C and C-5 to $-N'-R$. Such differences persist even among those imidazoles that do not carry a nitro group, e.g. **3-5**, **32** or those that carry a halogen instead, e.g. **6a**, (**6b**, δ C-4 121.0 is an exception) although the ranges are not as sharply defined.

In the case of the 1-substituted-2-nitroimidazoles, the distinction between C-4 and C-5 practically vanishes, cf. **26** vs **27** and **28**. **29** is a 2-nitro-4-substituted imidazole with C-4 and C-5 separated by about 4.2 ppm; this difference however is due to the fact that one of them is a quaternary C-atom. δ C-4 of **37** is also found to be similar to those in **26-28**.

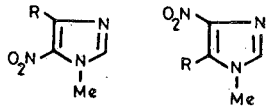
It is interesting to examine N-unsubstituted imidazoles, which are capable of tautomerism. In imidazole (**1**) and 2-methylimidazole (**2**), C-4 and C-5 are equivalent and have chemical shifts of 121.9 and 121.3 respectively. Their respective mono nitro-derivatives **7** and **9** and 2-chloro-4-nitroimidazole (**17**) can have either structure (**a**) or (**b**) or an equilibrium mixture of the two. The chemical shifts of the carbon atom in these molecules exhibiting a large one-bond



24c

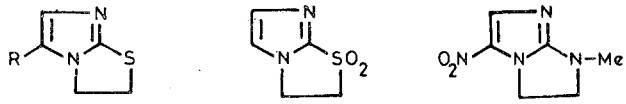


38



a b

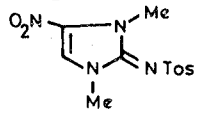
Compound No	R
39	Cl
40	I
41	-N O



42 R = H

43 R = NO_2

44 45



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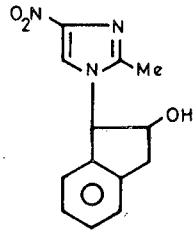


47

coupling* are respectively 118.6, 119.1 and 120.8 respectively, placing them largely, if not exclusively, in series-b [i.e. 1(H)-4-nitro]. This is further supported by solvent-induced shift studies in their ^{1}H NMR spectra (*vide infra*). 2-Nitro-4-substituted imidazoles, e.g. **29** are also capable of similar tautomeric formulations, but our data are too meagre for allowing valid decisions.

^{13}C chemical shifts and three-bond couplings have also been tested for structural assignments in the case of the bicyclic nitroimidazoles **43** and **45**, wherein the nitro group was introduced by nitration of the basic framework and oriented largely by analogy[18]. In their ^{13}C NMR spectra, the carbon signal exhibiting $^1J_{CH}$ coupling was located respectively at 136.8 and 137.9 respectively. These values occurring at even lower fields compared to series-a suggested that the orientations were indeed correct; the corresponding carbon centre in one precursor **42** was located at 133.7, compared to a value of 128.7 in the acyclic analogue **32**. These large doublets in **43** and **45** did not exhibit further three-bond splitting which was in apparent agreement with the structures proposed. However, neither of the carbon signals in the spectrum of **42** at 133.7 or 116.8, particularly the former exhibited a long range coupling with the methylene protons on the nitrogen atom. This indicates a structural constraint for the observation of long range coupling in such situations, with rigidity precluding the interaction that a freely rotating alkyl group allows. We have observed a similar absence of three-bond coupling in 5:6 fused bicyclic systems also[13].

*In the case of **7**, C-4 was distinguished from C-2 using the difference in $^1J_{CH}$ values.

^{1}H NMR Studies

The spectra were run separately in $CDCl_3$ and DMSO-d_6 and the results are recorded in Table 2. It was first ascertained in the cases of **8b** and **35b** that concentration had negligible effect on the chemical shifts of the carbon-bound protons.

The PMR spectra in $CDCl_3$ exhibited, in general, the C-4 proton in series-a to be more deshielded than C-5H in series-b; but the difference was slight, ranging from 0.06 ppm (**15**) to 0.25 ppm (**34**). Differentiation would require the availability of both the isomers and sufficient solubility in $CDCl_3$ for screening in CW (non-FT) instruments. In DMSO-d_6 however, δ C-5H of series-b were larger than those of C-4H in series-a. The spectra in $CDCl_3$ again revealed as expected and reported, methyl or methylene protons on N-1 to be deshielded by the adjacent NO_2 group (C-5 in series-a) by 0.04-0.46 ppm relative to their positions in series-b, where the NO_2 group is not adjacent. However, the small value of the lower limit of the range precluded the use of such data for structure assignment when both isomers were not available.

Reports[6,19] in the literature indicated that in N-alkylazoles (e.g. imidazole, pyrazole, triazole), DMSO-d_6 (and water) causes a larger downfield shift of protons alpha to the alkylated nitrogen atom than of nonadjacent heteroaromatic protons, relative to their respective positions in $CDCl_3$. A very small number of isomeric 1-alkyl-4- and 5-nitroimidazoles have been subjected to this study. For a number of N-substituted imidazoles, $\Delta\delta$ (DMSO-d_6 – $CDCl_3$) of $\pm$0.10 for C-4H, 0.10-0.60 for C-5H and C-2H have been recorded, and the claim made that in 20 cases studied there have been no exceptions to this rule[6]. Having a large number of isomeric pairs in our hands, we extended this study with the objectives of (i) assessing the validity of the above conclusion, (ii) probing whether absolute δ values rather than $\Delta\delta$ (DMSO-d_6 – $CDCl_3$) could be used for placement of a candidate nitroimidazole in

Table 2—^{1}H NMR Data for Nitroimidazoles*

Compd	δ $CDCl_3$				δ DMSO-d_6				Δδ (DMSO-d_6 − $CDCl_3$)		
	H-2	H-4	H-5	Others	H-2	H-4	H-5	Others	H-2	H-4	H-5
3	7.40 (*bs*)	7.03 (*m*)	6.88 (*m*)	N−CH_3, 3.67	7.57 (*bs*)	6.89 (*bs*)	7.10 (*bs*)	N−CH_3, 3.64	0.17	−0.14	0.23
4	—	6.83 (*d*)	6.76 (*d*)	N−CH_3, 3.53; 2−CH_3, 2.33	—	6.69 (*d*)	6.97 (*d*)	N−CH_3, 3.51; 2−CH_3, 2.24	—	−0.14	0.21
6a	7.42	6.85	—	N−CH_3, 3.55	7.83	7.05	—	N−CH_3, 3.68	0.41	0.2	—
6b	7.30	—	6.83	N−CH_3, 3.63	7.65	—	7.30	N−CH_3, 3.74	0.35	—	0.47
7	7.59**	—	7.95 (*d*)	—	7.88	—	8.33	—	0.29	—	0.38
8a	7.60	7.97	—	N−CH_3, 4.02	8.04	8.04	—	N−CH_3, 3.96	0.44	0.07	—
8b	7.43	—	7.78	N−CH_3, 3.83	7.82	—	8.36	N−CH_3, 3.79	0.39	—	0.58
9	—	—	7.76	2−CH_3, 2.42	—	—	8.20	2−CH_3, 2.36	—	—	0.44
10a	—	7.90	—	N−CH_3, 3.91; 2−CH_3, 2.48	—	7.94	—	N−CH_3, 3.81; 2−CH_3, 2.53	—	0.04	—
10b	—	—	7.67	N−CH_3, 3.68; 2−CH_3, 2.43	—	—	8.27	N−CH_3, 3.65; 2−CH_3, 2.44	—	—	0.60
11a	—	8.04	—	ArH, 8.44 (2H, *m*), 7.47 (2H, *m*), 2−CH_3, 2.29	—	8.23	—	ArH, 8.42 (2H, *m*); 2−CH_3, 2.21	—	0.19	—
11b	—	—	7.89	ArH, 8.47 (2H, *m*); 7.58 (2H, *m*); 2−CH_3, 2.47	—	—	8.49	ArH, 8.42 (2H, *m*); 7.89 (2H, *m*), 2−CH_3, 2.38	—	—	0.60
12a	7.65	7.98	—	1−CH_2, 4.47 (*t*); O−CH_2, 3.66(*m*); 1−CH_2−CH_2, 2.72(*t*); O−CH_2−CH_2, 2.42 (*m*)	8.06	8.06	—	1−CH_2, 4.46 (*t*); O−CH_2, 3.50 (*m*); 1−CH_2CH_2, 2.62 (*t*); O−CH_2CH_2, 2.39 (*m*)	0.41	0.08	—
12b	7.54 (*d*)	—	7.91 (*d*)	1−CH_2, 4.13 (*t*); OCH_2, 3.71 (*m*); 1−CH_2CH_2, 2.75 (*t*); O−CH_2CH_2, 2.51 (*m*)	7.85 (*d*)	—	8.40 (*d*)	1−CH_2, 4.19 (*t*); O−CH_2, 3.52 (*m*); 1−CH_2CH_2, 2.67 (*t*); O−CH_2CH_2, 2.42 (*m*)	0.31	—	0.49
13a	—	7.93	—	1−CH_2, 4.49 (*t*); O−CH_2, 4.00 (*t*); 2−CH_3, 2.54	—	8.05	—	1−CH_2, 4.45 (*t*); O−CH_2, 3.78 (*t*); 2−CH_3, 2.54	—	0.12	—
13b	—	—	7.73	1−CH_2 and OCH_2, 4.03; 2−CH_3, 2.43	—	—	8.22	1−CH_2, 3.93 (*t*); O−CH_2, 3.67 (*t*); 2−CH_3, 2.31	—	—	0.49
14a	—	7.82	—	2−CH_3, 2.50; CH_3CH, 1.33(*d*)†	—	8.05	—	2−CH_3, 2.50; CH_3CH, 1.18 (*d*)†	—	0.23	—
14b	—	—	7.72	2−CH_3, 2.43; CH_3−CH, 1.33 (*d*)†	—	—	8.21	2−CH_3, 2.36; CH_3CH, 1.10 (*d*)†	—	—	0.49
15a	—	7.82	—	2−CH_3, 2.51††	—	8.07	—	2−CH_3, 2.51††	—	0.25	—
15b	—	—	7.76	2−CH_3, 2.46††	—	—	8.23	2−CH_3, 2.38††	—	—	0.47
16a	—	7.97	—	1−CH_2, 4.78 (*t*); 1−CH_2CH_2, 3.45(*t*); CH_2CH_3, 3.06 (*q*); 2−CH_3, 2.61; CH_3CH_2, 1.42 (*t*)	—	8.03	—	1−CH_2, 4.70 (*t*); 1−CH_2CH_2, 3.67 (*t*); CH_2CH_3, 3.19 (*q*); 2−CH_3, 2.51; CH_3CH_2, 1.24 (*t*)	—	0.06	—

(*Contd*)

Table 2—^{1}H NMR Data for Nitroimidazoles* —(*Contd*)

Compd	δ $CDCl_3$				δ DMSO – d_6				Δδ (DMSO – d_6 – $CDCl_3$)		
	H-2	H-4	H-5	Others	H-2	H-4	H-5	Others	H-2	H-4	H-5
16b	—	—	7.79	1 – CH_2, 4.50 (*t*); 1 – CH_2CH_2, 3.39 (*t*); CH_2CH_3, 2.99 (*q*); 2 – CH_3, 2.51; CH_3CH_2, 1.42 (*t*)	—	—	8.39	1 – CH_2, 4.45 (*t*); 1 – CH_2CH_2, 3.73 (*t*); CH_2CH_3, 3.16 (*q*); 2 – CH_3, 2.42; CH_3CH_2, 1.25 (*t*)	—	—	0.60
17	—	—	7.87**	—	—	—	8.43	—	—	—	0.56
18a	—	7.92	—	N – CH_3, 4.00	—	8.11	—	N – CH_3, 3.89	—	0.19	—
18b	—	—	7.76	N – CH_3, 3.76	—	—	8.52	N – CH_3, 3.71	—	—	0.76
20a	—	7.86	—	O – CH_2, 3.92 (*m*); N – CH_3, 3.76; N – CH_2, 3.27 (*m*)	—	7.96	—	O – CH_2, 3.73 (*m*); N – CH_3, 3.66; N – CH_2, 3.16 (*m*)	—	0.10	—
21a	—	7.90	—	CH_2CH_2, 4.09; N – CH_3, 3.88; SO_2CH_3, 3.34	—	8.10	—	CH_2CH_2, 4.01; N – CH_3, 3.76; SO_2CH_3, 3.38	—	0.20	—
21b	—	—	7.68	CH_2CH_2, 4.10; N – CH_3, 3.76; SO_2CH_3, 3.33	—	—	8.42	CH_2CH_2, 4.00; N – CH_3, 3.66; SO_2CH_3, 3.39	—	—	0.74
26	—	—	—	—	—	7.37	7.37	—	—	—	—
27	—	7.17	7.20	—	—	7.19	7.67	—	—	0.02	0.47
28	—	7.12 (*d*)**	7.30 (*d*)	N – CH_2, 4.80 (*dxd*); 4.33 (*dxd*); – CH – OH, 4.17 (*m*); – CH_2Cl, 3.55 (*d*); – OH, 5.44 (*bs*)	—	7.16 (*d*)	7.58 (*d*)	N – CH_2, 4.03 (*dxd*); 4.31 (*dxd*); – CHOH, 4.08 (*m*); – CH_2Cl, 3.61 (*d*); – OH, 5.67 (*bs*)	—	0.04	0.28
30a	—	8.05	—	N – CH_3, 4.45	—	8.20	—	N – CH_3, 4.20	—	0.15	—
30b	—	—	7.88	N – CH_3 4.22	—	—	8.73	N – CH_3, 4.07	—	—	0.85
31a	—	7.83	—	N – CH_3, 4.21; O – CH_3, 3.80	—	7.88	—	N – CH_3, 4.08; O – CH_3, 3.64	—	0.05	—
31b	—	—	7.63	N – CH_3, 4.17; O – CH_3, 3.58	—	—	8.10	N – CH_3, 4.00; OCH_3, 3.43	—	—	0.47
32	—	6.73	6.73	N – CH_3, 3.43; S – CH_3, 2.47	—	6.90 (*d*)	7.13 (*d*)	N – CH_3, 3.53; S – CH_3, 2.50	—	0.17	0.40
33	—	7.00 (*d*)	7.03 (*d*)	N – CH_3, 3.97; SO_2CH_3, 3.33	—	7.07 (*d*)	7.42 (*d*)	N – CH_3, 3.90; SO_2CH_3, 3.33	—	0.37	0.39
34a	—	8.01	—	N – CH_3, 3.87; S – CH_3, 2.73	—	8.13	—	N – CH_3, 3.77; S – CH_3, 2.67	—	0.12	—
34b	—	—	7.76	N – CH_3, 3.65; S – CH_3, 2.71	—	—	8.44	N – CH_3, 3.62; S – CH_3, 2.61	—	—	0.68
35a	—	7.95	—	N – CH_3, 4.29; SO_2CH_3, 3.47	—	8.13	—	N – CH_3, 4.10; SO_2CH_3, 3.46	—	0.18	—
35b	—	—	7.82	N – CH_3, 4.09; SO_2CH_3, 3.49	—	—	8.68	N – CH_3, 4.01; SO_2CH_3, 3.49	—	—	0.86
36b	8.38 (*d*)	—	8.52 (*d*)	—	8.98 (*d*)	—	9.40	—	0.60	—	0.88
37a	—	7.73	—	CH_2CH_3, 4.39 (*q*); N – CH_3, 4.35; CH_2CH_3, 1.41 (*t*)	—	7.78	—	CH_2CH_3, 4.38 (*q*); N – CH_3, 4.18; CH_2CH_3, 1.32 (*t*)	—	0.05	—

(*Contd.*)

Table 2—^{1}H NMR Data for Nitroimidazoles* —(*Contd*)

Compd	δ $CDCl_3$				δ DMSO – d_6				$\Delta\delta$ (DMSO – d_6 – $CDCl_3$)		
	H-2	H-4	H-5	Others	H-2	H-4	H-5	Others	H-2	H-4	H-5
38	—	—	—	N–CH_2, 4.08; O–CH_2, 3.67 (*m*); 4–CH_2, 3.61; 5–CH_2, 3.49; N–CH_2, 2.49 (*m*)	—	—	—	N–CH_3, 3.96; 4–CH_2, 3.62; O–CH_2, 3.53 (*m*); 5–CH_2, 3.41; N–CH_2, 2.51 (*m*); 2.39 (*m*)	—	—	—
39a	7.50	—	—	N–CH_3, 4.03	8.07	—	—	N–CH_3, 3.94	0.57	—	—
39b	7.48	—	—	N–CH_3, 3.73	7.99	—	—	N–CH_3, 3.72	0.51	—	—
40a	7.26	—	—	N–CH_3, 4.03	8.00	—	—	N–CH_3, 3.92	0.74	—	—
40b	7.69	—	—	N–CH_3, 3.75	8.10	—	—	N–CH_3, 3.70	0.41	—	—
41a	7.27	—	—	N–CH_3, 3.94; O–CH_2, 3.85 (*m*); N–CH_2, 3.53 (*m*)	7.85	—	—	N–CH_3, 3.84; O–CH_2, 3.71 (*m*); N–CH_2, 3.41 (*m*)	0.58	—	—
41b	7.29	—	—	O–CH_2, 3.85 (*m*); N–CH_3, 3.62; N–CH_2, 3.18 (*m*)	7.62	—	—	O–CH_2, 3.73 (*m*); N–CH_3, 3.57; N–CH_2, 3.11 (*m*)	—	—	—
42	—	6.96 (*d*)	6.93 (*d*)	N–CH_2, 4.14 (*m*); S–CH_2, 3.78 (*m*)	—	6.85 (*d*)	7.20 (*d*)	N–CH_2, 4.15 (*m*); S–CH_2, 3.86 (*m*)	—	0.11	0.24
43	—	7.89	—	N–CH_2, 4.65 (*t*); S–CH_2, 3.95 (*t*)	—	7.97	—	N–CH_2, 4.62 (*t*); S–CH_2, 4.05 (*t*)	—	0.08	—
44	—	7.35 (*d*)	7.06 (*d*)	N–CH_2, 4.54 (*m*); S–CH_2, 3.94 (*m*)	—	7.51 (*d*)	7.30 (*d*)	N–CH_2, 4.57 (*m*); S–CH_2, 4.16 (*m*)	—	0.16	0.24
45	—	7.70	—	N–CH_2, 4.35 (*m*); N–CH_2, 3.94 (*m*); N–CH_3, 3.02	—	7.86	—	N–CH_2, 4.30 (*m*); N–CH_2, 3.90 (*m*); N–CH_3, 2.89	—	0.16	—
46	—	7.69	—	N–CH_3, 3.78, 3.72; ArH, 7.27 (*m*); 7.83 (*m*); $ArCH_3$, 2.41	—	8.55	—	N–CH_3, 3.63, 3.50; ArH, 7.27 (*m*), 7.70 (*m*); $ArCH_3$, 2.37	—	0.86	—

*All peaks are singlets unless otherwise stated. Multiplicities are given in parentheses, δ in ppm.
**Compound insoluble in $CDCl_3$; a concentrated DMSO – d_6 solution was diluted with excess $CDCl_3$
†CH_2–CH– not analysed
††$ClCH_2$–CH–CH_2 not analysed.

either series, (iii) investigating whether pairs are necessary for unambiguous identification and (iv) understanding the origin of DMSO induced shifts.

The data presented in Table 2 do indeed support the claims. In the group of 1-substituted-4-nitroimidazoles (series-b) $\Delta\delta$ ranged from 0.47 ppm (**6b**, **15b**, **31b**) to 0.88 ppm (**36b**) and in the group of 5-nitro isomers (series-a) from 0.04 ppm (**10a**) to 0.25 ppm (**15a**). It appears thus possible to conclude that in such molecules, observation of $\Delta\delta$ values of above 0.45 ppm for the nitroimidazole proton would warrant orienting the nitro group at position-4 (series-b) and molecules showing $\Delta\delta$ values of less than 0.3 ppm would be 5-nitroimidazoles (series-a). 2,4-Dinitroimidazole yields the same alkyl derivative, **30b** as the major product under acidic, neutral or alkaline conditions. This exhibits a $\Delta\delta$ value of 0.85 ppm and the minor product, 0.15 ppm, clearly placing the former in series-b and the latter in series-a. It is also interesting to note that even with 1-aryl substituted nitroimidazoles, the rule applies: $\Delta\delta$ for **11a**, 0.19; for **11b**, 0.60 ppm. Assuming that it would extend to bicyclic nitroimidazoles, the small $\Delta\delta$ values obtained for **43** (0.08 ppm) and **45** (0.16 ppm) would support the given orientation of the NO_2 group, indicated earlier by ^{13}C studies.

Among the compounds studied, there were a few with no substituent at position-2: **8a**, **b**; **12a**, **b**; and **36b**. Interestingly, the proton at position-2 suffered a downfield shift in *both* the series going to DMSO-d_6 from $CDCl_3$, $\Delta\delta$ being as follows: series-a, 0.44, 0.41; series-b, 0.39, 0.31, 0.60. There were also three isomeric pairs, **39a**,**b**, **40a**,**b** and **41a**,**b**, having a proton at position-2 and an extra substituent at position 4 or 5 (as the case may be). In this group, the respective $\Delta\delta$ values were: series-a, 0.57, 0.74, 0.58; series-b, 0.51, 0.41, 0.33. Thus $\Delta\delta$ for protons at C-2 in nitroimidazoles is seen to range from 0.30 to 0.75 ppm.

To gain insight into the origin of these $\Delta\delta$ values, it was of interest to look at some imidazoles carrying groups other than nitro-: Cl, Me etc., e.g. **3**, **4**, **6**, **32**, **33** and **42**. Except in the case of **6**, we had difficulty in assigning protons at C-4 and C-5 unambiguously and for **3** and **4** we relied on literature data[6]. Based upon these assignments, it was observed that in the haloimidazoles **6a** and **6b**, $\Delta\delta$ for C-2H was 0.41 and 0.35 ppm respectively, $\Delta\delta$ for C-4H in **6a** was 0.20 ppm and for C-5H in **6b**, 0.47 ppm. In 2-sulphur substituted compounds, the following were observed: **32**, $\Delta\delta$ for C-4H, 0.17 and for C-5H, 0.40 ppm; **42**, $\Delta\delta$ for C-4H, -0.11 and for C-5H, 0.24 ppm; **44**, $\Delta\delta$ for C-4H, 0.16 and for C-5H, 0.24 ppm. Corresponding shifts for **3** and **4** were smaller. It was thus clear that DMSO-d_6 induced shifts of C-5H in substituted imidazoles are accentuated by the presence of electron withdrawing groups in the molecule.

We then looked at $\Delta\delta$ values of C-5H in series-b as a function of the group (or atom) at position 2 (Table 3). Unfortunately, we were unable to synthesise **20b** which would have completed this series. Nevertheless, Table 3 clearly indicates a trend of increasing $\Delta\delta$ values with increasing electronegativity of the group X.

Based upon all these observations and also the relatively negligible solvent effect on other protons in these molecules (mostly slight upfield shifts), a tentative explanation for the large value of $\Delta\delta$ (DMSOd_6 – $CDCl_3$) for C-5 protons in series-b, small values of C-4 protons in series-a and again large ones for C-2 protons in both the series appears to be the one invoking the coordination of the lone pair of electrons on the substituted N-atom of the imidazole with the positively charged sulphur atom of DMSO and a consequent inductive desheilding of adjacent C-2 proton in series-a and b and C-5 protons in the latter, while in series-a, C-4H, being further removed is relatively unaffected**. The propensity for coordination perhaps gets augmented by the electrostatic attraction between the negative oxygen atoms of DMSO and the electron-withdrawing substituent at position-2 and/or 5. A pertinent observation in this connection is that the coordination is not seriously influenced by the size of the substituent on the nitrogen atom as evident from the data in Table 4, although crowding (e.g. **47**)[20] seems to have a slight deleterious effect. It is also likely that compared to **13b**, **14b** and **15b**, **16b** with a similar 1-alkyl chain causes a larger shift due to some secondary influence of the SO_2 group in a favoured conformation.

Looking solely at δ values of nitroimidazoles in DMSO-d_6 of C-4H in series-a (7.88-8.23 ppm) and C-5H in series-b (8.10-9.40 ppm), it is obvious that there is an overlap and that the ^1H NMR spectrum of an unknown nitroimidazole in DMSO-d_6 cannot alone provide unambiguous structural information.

Nitroimidazoles (**7**, **9** and **17**) are capable of tautomerism and as discussed in the previous section dealing with ^{13}C studies can fall into series-a or b depending upon the location of the nitrogen-bound proton or can be an equilibrium mixture. Their chemical shifts in DMSO-d_6 (8.33, 8.40, 8.43) and $\Delta\delta$ values (0.38, 0.44, 0.56) place them largely if not solely, in series-b, supporting the deduction from ^{13}C studies.

The prominent solvent-induced shift is also observed for nitroimidazoles: thus **46** shows a $\Delta\delta$ value of 0.86 ppm, nearly equalling the maximum shift observed for the aromatic nitroimidazoles of series-b.

**This however fails to explain the reported similar water-induced shifts. An alternative explanation requiring a direct bonding of hydrogen atoms with oxygen atom of the solvents would require that the acidities decrease in the following order: C-5H > C-2H > C-4H.

Table 3—Mass Spectra of Nitroimidazoles*

Compd	Mass peaks (% intensity)** at					
	M^+	$M^+ - O$	$M^+ - OH$	$MH^+ - NO$	$M - NO$	$M - NO_2$
7	113	97(22)	96(††)	94(††)	93(28)	67(100)
8a	127	111(15)	110(42)	98(101)	97(25)	81(80)
8b	127	111(15)	110(††)	98(1)	97(69)	81(20)
9	127	111(12)	110(††)	—	—	81(150)
10a	141	125(††)	124(††)	112(††)	111(4)	95(120)
10b	141	125(††)	124(††)	112(††)	111(††)	95(12)
11a	248	232(20)	231(††)	219	218(3)	202(110)
11b	248	232(††)	231(††)	219(††)	218(††)	202(500)
12a	226	210(25)	209(135)	197(††)	196(12)	180(500)
12b	226	210(30)	209(5)	197(††)	196(20)	180(††)
13a	171	155(3)	154(24)	—	141(5)	125(200)
13b	171	155(8)	154(††)	142(6)	141(88)	125(9)
14a	185	169(48)	168(20)	156(††)	155(††)	139(30)
14b	185	169(100)	168(††)	156(5)	155(5)	139(5)
15a†	219	203(2)	202(20)	190(††)	189(††)	173(100)
15b†	219	203(7)	202(††)	190(††)	189(††)	173(††)
16a	247	231(5)	230(30)	218(††)	217(6)	201(800)
16b	247	231(13)	230(35)	218(10)	217(3)	201(4)
21a	289	273(††)	272(††)	260(7)	259(50)	243(††)
21b	289	273(7)	272(35)	260(††)	259(5)	243(††)
30a	172	156(4)	155(4)	143(5)	142(33)	126(††)
30b	172	156(15)	155(††)	143(4)	142(55)	126(4)
39a†	161	145(4)	144(10)	132(25)	131(45)	115(10)
39b†	161	145(4)	144(††)	132(††)	131(13)	115(55)
40a	253	237(6)	236(15)	224(19)	223(22)	207(12)
40b	253	237(3)	236(††)	224(††)	223(2)	207(2)

*Mass spectra were run on a Varian Mat CH 7 spectrometer generally using 70/eV and temperatures appropriate to the ionisation of compounds studied.

**Intensities are approximate and relative to M^+ peak as 100%.

†Mass peaks reported for ^{35}Cl.

††Negligible intensities.

Table 4—UV Spectra of Nitroimidazoles

Compd	λ_{max} (nm) (log ε) in					
	95% EtOH	95% EtOH + H_2SO_4	95% EtOH (or distilled water) + NaOH	Distilled water	N/10 H_2SO_4	1N H_2SO_4
7	287(3.74)	—	347(3.98)	296(3.76)	296(3.75)	281(3.70)
8a	296(3.90)	—	296(3.92)	304(3.93)	266(3.75)	265(3.79)
8b	289(3.84)	—	289(3.87)	301(3.83)	300(3.85)	297(3.80)
9	299(3.79)	—	363(4.07)	310(3.82)	296(3.70)	278(3.84)
10a	310(3.95)	—	310(4.01)	320(3.95)	276(3.82)	276(3.82)
10b	301(3.84)	—	301(3.88)	314(3.89)	310(3.82)	281(7.84)
11a	258(4.05), 291(4.03)	—	—	—	—	—
11b	290(4.19)	—	—	—	—	—
12a	299(3.85)	—	—	304(3.86)	299(3.81)	268(3.78)
12b	291(4.17)	—	—	298(3.86)	293(3.87)	292(3.85)
13a	313(3.96)	—	—	319(3.96)	276(3.82)	276(3.87)
13b	302(3.87)	—	—	313(3.90)	310(3.83)	283(3.81)
14a	313(3.92)	—	—	319(4.00)	277(3.76)	277(3.79)
14b	302(3.88)	—	—	312(3.87)	311(3.87)	285(3.86)
15a	310(3.95)	—	—	318(3.96)	276(3.80)	276(3.80)
15b	300(3.87)	—	—	311(3.92)	310(3.82)	287(3.73)
16a	310(3.96)	—	—	317(3.96)	278(3.78)	276(3.81)
16b	297(3.83)	—	—	307(3.89)	307(3.93)	296(3.79)

(Contd)

Table 4—UV Spectra of Nitroimidazoles—(*Contd*)

Compd	λ_{max} (nm) (log ε) in					
	95% EtOH	95% EtOH + H_2SO_4	95% EtOH (or distilled water) + NaOH	Distilled water	N/10 H_2SO_4	1N H_2SO_4
20a	355(3.94)	—	374(3.79)	374(4.00)	339(3.79)	334(3.57)
21a	316(3.95)	—	316(3.87)	318(3.95)	319(3.96)	316(3.93)
21b	303(3.81)	—	303(3.81)	309(3.83)	307(3.83)	308(3.85)
22a	317(3.88)	317(3.88)	385(3.93)	329(3.83)	—	—
23a	310(3.93)	310(3.93)	389(4.12)	315 (qualitative)	—	—
24a	360(3.87)	356(3.88)	399(4.00)	390(3.89)	—	—
25a	308(4.01)	307(4.02)	307(4.09)	312 (qualitative)	—	—
26	314(3.92)	—	367(4.09)	324(3.93)	—	—
28	316(3.80)	—	316(3.89)	325(3.83)	325(3.83)	323(3.81)
32	249(3.59)	—	249(3.70)	247(3.57)	251(3.78)	250(3.65)
34a	348(3.88)	—	—	—	—	—
34b	333(3.74)	—	—	—	—	—
35a	289(3.94)	—	—	—	—	—
35b	278(3.85)	—	—	—	—	—
39a	302(3.88)	—	—	—	—	—
39b	296(4.12)	—	—	—	—	—
40a	256(3.62), 321(3.81)	—	—	—	—	—
40b	315(3.85)	—	—	—	—	—
41a	273(3.77), 385(3.94)	—	—	—	—	—
41b	289(3.50) 350(3.35)	—	—	—	—	—
44	231(3.86)	231(3.88)	231(3.91)	—	—	—
45	390(4.04)	—	340(3.90)	345(3.01) 415(3.71)	365(3.53)	363(3.31)
46	340(3.78)	340(3.79)	301(4.10) 370(3.59)	324 (qualitative)	—	—

We also made a limited study of solvent-induced proton shifts in a few 2-nitroimidazoles, **26-28**, **37** and **38**. The assignments of C-4 and C-5 protons in **27** and **28** were again not easy; the values given are based on the shifts reported[6] for **27**. Both the compounds showed larger $\Delta\delta$ values for C-5H than for C-4H. **37** was synthesised by an unambiguous route involving the oxidation of ethyl 1-methyl-2-amino-5-carboxylate. As expected, $\Delta\delta$ for C-4H was minimal in **37**, **38**, having no imidazole protons, exhibited slight upshield shifts for the protons present.

Mass Spectral Studies

Aromatic nitro compounds as well as carboxylic acids are known to exhibit in their mass spectra, an important fragment with m/z at M − OH, when the *ortho*-position has a proton-bearing substituent, like amino, alcohol or alkyl groups. In this process, the hydrogen atom is abstracted by the oxygen atom via a cyclic mechanism[21]. We expected neighbouring group participation to occur in series-a but not in series-b and undertook a limited study. In Table 5 are presented fragments of only the pertinent nitro group—loss of O and NO by the known rearrangement of NO_2 to O − NO function and loss of OH by hydrogen abstraction from a neighbouring group (when operative). Our expectation was realized in that quite a few 1-alkyl-5-nitroimidazoles, such as **8a**, **12a-16a**, **39a** and **40a** showed $M^+ - OH$ peaks with an intensity (relative to M^+) ranging from 4-135%, with **10a** as an exception. The mass spectra of 1-unsubstituted-4-(5)-nitroimidazoles (**7**) and (**9**) as also of 1-aryl-5-nitroimidazole (**11a**) lacked the $M^+ - OH$ peak as expected. Most of the corresponding 4-nitroimidazoles of series-b lost OH to a smaller or negligible extent. There were important exceptions: the sulphone **16b** had a slightly more intense $M^+ - OH$ peak than **16a**, which is probably due to the participation of the sulphone oxygen atom. We believe that the same phenomenon is responsible for the inverted order in the case of **21a** and **21b** with the latter having this fragment (35%), but not the former. The diagnostic value of this mass spectral fragment, the formation of which is visualised in Scheme 1 is thus of doubtful

Table 5—Melting Points (corrected) and R_f Values of Nitroimidazoles

Compd	m.p. °C	R_f
8a	56-58	0.65[a]
8b	130-32	0.42[a]
10a	135-38	0.64[a]
10b	184-86	0.47[a]
11a	153-55	0.65[b]
11b	182-84	0.65[b]
12a	110-12	0.30[a]
12b	107-9	0.18[a]
13a	158-60	0.33[b]
13b	122-24	0.20[b]
14a	71-73	0.41[b]
14b	146-48	0.27[b]
15a	90-92	0.23[a]
15b	147-49	0.10[a]
16a	125-27	0.61[b]
16b	139-41	0.39[b]
18a	82-84	0.64[a]
18b	153-55	0.47[a]
21a	184-86	0.60[b]
21b	174-75	0.48[b]
30a	83-85	0.72[a]
30b	139-41	0.41[a]
31a	70-72	0.74[a]
31b	130-32	0.67[a]
35a	90-92	0.65[a]
35b	162-64	0.33[a]
39a	80-82	0.59[a]
39b	146-48	0.53[a]
40a	148-50	0.59[a]
40b	234-36	0.45[a]
41a	123-25	0.68[a]
41b	216-18	0.57[a]

(a) In $CHCl_3$ – MeOH (97:3)
(b) In $CHCl_3$ – MeOH (95:5)

utility. It is likely that the radical cation depicted actually undergoes ring expansion to a pyrimidine or a pyrazine[22].

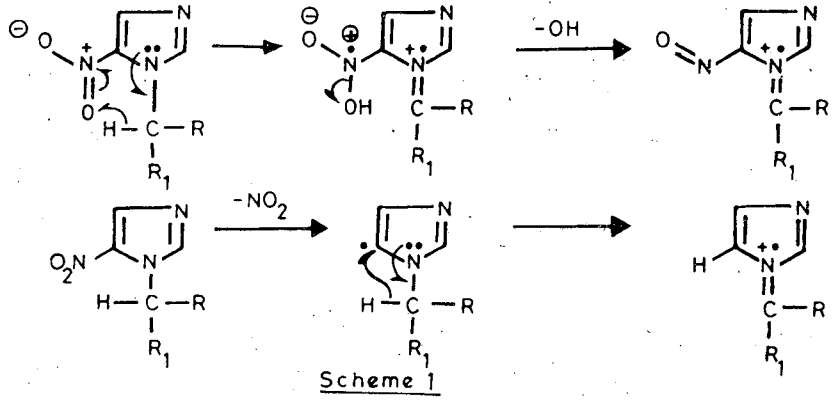
Interestingly, we also noted that the 5-nitroimidazoles showed a more intense $M^+ - NO_2$ fragment than their 4-nitro counterparts, e.g. **8a**, **10a**, **12a-16a** and **40a**, the strength of the peak ranging from 10-800%. Again there were exceptions -1-(*p*-nitrophenyl)-2-methyl-4-nitroimidazole (**11b**) (500%) and 5-nitro-isomer (**11a**) (110%); but this case is complicated by the presence of the second aromatic nitro group. **21a** and **21b**, as also **30a** and **30b** do not lose No_2 appreciably, perhaps due to the destabilisation of the radical cation by the substituent at position-2, while in the case of **39a** and **39b**, the order is in fact reversed. The generally favoured loss of NO_2 group in the series-a can perhaps be ascribed to the participation of imidazole nitrogen and hydrogen abstraction by C-5 after loss of the NO_2 group as shown in Scheme 1. The 1-unsubstituted nitroimidazoles (**7**) and (**9**) also form a relatively intense $M^+ - NO_2$ fragment.

Van Lear has noted an unusual rearrangement in the mass spectra of several 1-alkyl-2-heterocyclyl-5-nitroimidazoles[23], where the alkyl group at position-1 is lost together with the O atom of the nitro group, to give rise to 2-heterocyclyl-5-nitrosoimidazole radical ion as a prominent fragment. We find that this criterion can also be used generally for distinguishing between series-a and b with some exceptions. Thus the mass spectra of **13a** and **16a** did not have any major ion at *m/z* 111.

UV Spectral Studies

Indications are available in the literature to show that 1-alkyl-5-nitroimidazoles have maxima at slightly longer wavelengths compared to the 4-nitro-isomers[5]. A somewhat more useful technique is the differential hypsochromic shifts exhibited by these compounds in acid[5]. In one case e.g. **7a**, 1 *M* $HClO_4$ is claimed to produce a marked hypsochromic shift, which **7b** experiences only with 5 *M* $HClO_4$ (ref. 24). In another pair **12a** and **12b**, 0.1 *N* H_2SO_4 is reported to produce a hypsochromic change in the former, but not in latter[25]. We have probed these observations further with the materials at our disposal and expanded the study to cover other kinds of nitroimidazoles which have basic and acidic centres.

The UV spectra were recorded in neutral, alkaline and acidic conditions. Data presented in Table 4 allow the following conclusions:



Scheme 1

1-Substituted-5-nitroimidazoles (series-a) as a rule exhibit λ_{max} in ethanol at slightly longer wavelength (7-13 nm) compared to the 4-nitro-isomers of series-b; **11a** and **11b** are exceptions, presumably due to the presence of a *p*-nitrophenyl group at position-1. λ_{max} in water of isomeric pairs studied occurs at longer wavelengths in both the series by 5-13 nm, with **21a** as an exception (12 nm). In the more basic 5-nitroimidazole series[5], the absorption maxima undergo a marked hypsochromic shift (35-44 nm) in 0.1 *N* H_2SO_4 as a result of the imidazole nitrogen accepting a proton and (perhaps) partial loss of conjugation with the nitro group. With series-b, this does not happen in 0.1 *N* H_2SO_4 and often incompletely in 1 *N* H_2SO_4. Two exceptions are worth recording and discussing. The methanesulphonyl-imidazolidinone moiety at position-2 in **21a** and **21b** apparently reduces the basicity so much that even 1 *N* H_2SO_4 is unable to protonate the imidazole (Steric hindrance to protonation is not ruled out). 1-(Morpholinoethyl)-5-nitroimidazole (**12a**) and the 4-nitroisomer (**12b**) are reported in the literature[25] to be differentiated in their UV spectra in 0.1 *N* H_2SO_4. We could not reproduce these observations (Personal communication from Dr George). However, 1 *N* H_2SO_4 could bring about the expected change in **12a**; **12b** is relatively unaffected even under these conditions. The explanation for the different behaviour of **12a** (compared to **13a-16a**) must lie in the fact that the side-chain morpholine accepts the first proton and much lower *p*H is required to load the second proton on to the nitroimidazole moiety. 2-Methyl-4(5)-nitroimidazole (**9**) carrying no substituent at position-1 appears to be a weaker base than **13a-16a** since significant hypsochromic effect occurs only in 1 *N* H_2SO_4. Its desmethyl derivative (**7**) is only partly protonated even in 1 *N* H_2SO_4.

The absorption maxima of both **7** and **9**, but not the 1-alkylated derivatives (**8a**, **8b**; **10a**, **10b**; **21a**, **21b**) undergo the expected pronounced bathochromic shift (60, 64 nm) in alcoholic sodium hydroxide solution due to the formation of the conjugated nitroimidazole anion.

2-Nitroimidazole (**26**) and a 1-substituted derivative (**28**) were also studied in this respect. Both show λ_{max} at longer wavelengths in water compared to those in alcohol. **28** is so feebly basic that no change occurs in the λ_{max} even in 1 *N* H_2SO_4. **26** forms an anion in alcoholic alkali which shows a maximum at a longer wavelength (by 53 nm) compared to neutral solution.

1-Methyl-2-morpholino-5-nitroimidazole (**20a**) with the basic residue in conjugation with the nitro group has λ_{max} (ethanol) at longer wavelength (355 nm) compared to the ones discussed earlier, exhibiting a further bathochromic shift in water. Surprisingly, even 1 *N* H_2SO_4 is unable to protonate the morpholine fully (374→334 nm). The bathochromic shift of 19 nm in alcohlic alkali is not understood. 2-Acylamino derivatives (**22a**) and (**23a**) as well as the N-methylsulphonamide (**25a**) have this maximum shifted to shorter wavelengths in water (329, 315, 312 nm) and in ethanol (317, 310, 308 nm). As expected, none of the three is affected by alcoholic sulphuric acid but the maxima undergo a marked bathochromic shift in the case of **22a** and **23a** (λ_{max} 385 and 389 nm) in the presence of alkali due to the formation of the amide ion conjugated to a nitro group. **25** lacking an acidic proton on the amide group is naturally unaffected. The toluenesulphonamide (**24**) provides an interesting case. In ethanol solution, but even more so in water, λ_{max} occurs at very long wavelength (390 nm in water) which is only slightly less than in alcoholic alkali (399 nm). λ_{max} in ethanol (360 nm) matches the one found for 1,3-dimethyl-2-tosylimino-4-nitroimidazoline (**46**) (340 nm). Acid again does not disturb the observed maximum of **24** in ethanol alone. This is best explained by postulating that **24** exists largely in ethanol and almost completely in water in the imino form (**24c**), in contrast to the amides (**22**) and (**23**) which seem to prefer the 'amino' structure given. These conclusions are supported by ^{13}C NMR studies reported elsewhere[26].

The nitroimidoimidazole (**45**) has the distinction of having an absorption maximum at the longest wavelength (415 nm in water) of all compounds studied presently; as with **20a**, even 1 *N* H_2SO_4 destroys the conjugation of N-Me with the NO_2 group only partially (363 nm). The maximum at 390 nm in EtOH undergoes a hypsochromic shift to 340 nm in alkali due to a suspected cleavage of C-2-N-Me bond.

TLC Behaviour and Melting Points

We also took the opportunity to compare isomeric pairs of series-a and b in these parameters and the data are presented in Table 5. With a single exception of **11a** and **11b** having the same R_f, in all other cases, the 5-nitro-isomer had a larger R_f value than the 4-nitro-derivative. Interestingly although 5-nitroimidazoles are reported to be stronger bases than 4-nitroisomers[5] (we have not measured pK_as of our compounds), in the systems tried (silica gel; chloroform-X% MeOH), the former moved faster.

Compounds of series-a as a rule had lower melting points than those of series-b. Some exceptions are **12a**, **12b**; **13a**, **13b**; and **21a**, **21b**.

Conclusion

Our study reveals that ^{13}C NMR spectroscopy offers the best method to differentiate between isomeric 1-substituted-4- and 5-nitroimidazoles even

when only one isomer is available chemical shifts alone or in conjunction with signal multiplicity of the proton-bearing imidazole carbon atoms are useful for this purpose. DMSO-d_6 induced shifts of the imidazole protons relative to the shifts in $CDCl_3$ offer the next best possibility as an absolute diagnostic tool.

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