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4- AND 5-NITROIMIDAZOLES: ^{13}C NMR ASSIGNMENT OF STRUCTURE

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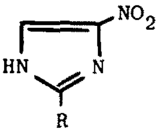
Abstract - The use of ^{13}C NMR spectroscopy has been found to provide a simple and unambiguous method for the assignment of the position of the nitro group in 1-substituted nitroimidazole derivatives.

Nitroimidazoles are compounds of very considerable commercial and chemotherapeutic importance. Clinical trials in 1960 showed that 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (METRONIDAZOLE) is a highly systemic trichomonacide and subsequent studies have established that this antiprotozoal activity of metronidazole extends to Entamoeba histolytica and Giardia lamblia; for these infestations - trichomoniasis, amoebiasis and giardiasis - metronidazole has become the treatment of choice. In addition, studies have also shown that the compound possesses broad-spectrum activity against anaerobic bacteria, whereas aerobic and facultative bacteria are generally resistant to it. The introduction of metronidazole and dimetridazole stimulated much synthetic chemistry on nitroimidazoles which resulted in the discovery of a number of compounds which have become important in the areas of human and/or animal health treatment.

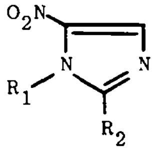
1-Substituted 4- and 5-nitroimidazoles have been prepared in a variety of ways, the most common of which is by alkylation of 4(5)-nitroimidazoles. The ultimate orientation of the nitro group, however, depends on a number of factors, the most important of which appear to be the nature of the alkylating agent used and the reaction conditions employed. The 5-nitro derivatives, however, generally possess significantly greater biological activity than the 4-nitro isomers and hence it is important that an unambiguous method of structure assignment be available. Previous attempts to provide

Table I. ^{13}C NMR Chemical Shifts of 4(5)-Nitroimidazoles[4]



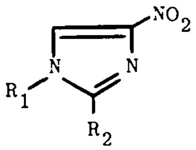
Compound	Ref.	Substituent R	Chemical Shifts (δ) values ppm C_2	C_4	C_5
1	5	H	136.7	149.2	119.8
2	5	CH_3	145.8	148.0	119.5
3	5	$CH(CH_3)_2$	153.75	147.2	118.92

Table II. ^{13}C NMR Chemical Shifts of 1-Substituted-5-Nitroimidazoles[4]



Compound	Ref.	Substituent		Chemical shift (δ) values ppm			
		R_1	R_2	C_2	C_4	C_5	2-CH_3
4	5	CH_3	H	143.52	133.11	139.45	-
5	6	$CH_2CO_2C_2H_5$	H	142.89	131.40	139.85	-
6	6	$CH_2CO_2C_2H_5$	CH_2OH	152.58	131.59	138.82	-
7	5	CH_3	CH_3	151.14	132.23	Not observed	13.68
8	5	$CH{=}CH_2$	CH_3	150.03	131.84	138.57	14.66
9	7	CH_2CH_2Br	CH_3	151.62	133.17	138.12	14.26
10	5	CH_2CH_2Cl	CH_3	151.90	133.20	138.48	14.25
11	5	CH_2CH_2OH	CH_3	151.09	132.90	138.54	14.20
12	7	CH_2CO_2H	CH_3	151.56	132.21	138.61	13.49
13	7	$CH_2CO_2CH_3$	CH_3	151.43	131.60	138.59	13.40
14	7	$CH_2CO_2C_2H_5$	CH_3	151.53	132.10	138.70	13.44
15	8	CH_3	$CH(CH_3)_2$	157.84	132.04	138.60	-

Table III. ^{13}C NMR Chemical Shifts of 1-Substituted-4-Nitroimidazoles[4]



Compound	Ref.	Substituent		Chemical shift (δ) values ppm			
		R_1	R_2	C_2	C_4	C_5	2-CH_3
16	5	CH_3	H	138.6	147.8	123.1	-
17	5	CH_3	CH_3	145.66	145.66	122.91	12.60
18	5	CH_2CH_3	CH_3	144.94	145.80	121.57	12.63
19	7	CH_2CH_2Cl	CH_3	145.16	145.76	121.79	12.05
20	5	CH_2CH_2OH	CH_3	145.69	145.46	122.44	12.75
21	7	CH_2CO_2H	CH_3	145.75	145.16	122.75	12.01
22	7	$CH_2CO_2CH_3$	CH_3	145.56	145.56	122.34	11.87
23	7	$CH_2CO_2C_2H_5$	CH_3	146.16	146.16	122.98	12.48
24	5	CH_2CH_2CN	CH_3	145.29	145.63	121.81	12.47
25	7	$CH_2CH_2CO_2H$	CH_3	145.37	145.62	121.89	12.62
26	7	$CH_2CH_2CO_2CH_3$	CH_3	145.23	145.66	121.59	12.36
27	5	$CH_2C_6H_5$	CH_3	145.14	145.14	122.48	12.85
28	9	$CO_2CH_2C_6H_5$	CH_3	147.29	145.80	119.31	16.34
29	9	$CO_2C_2H_5$	CH_3	147.34	145.87	119.31	16.39
30	9	$(C_6H_5)_3C$	CH_3	147.76	146.54	121.71	16.87
31	8	CH_3	$CH(CH_3)_2$	153.23	146.69	123.07	-

such a method have included the application of IR,[1] UV,[1] ^{1}H NMR,[1] and mass spectroscopic techniques,[2] and the use of pK_a[3] and polarographic measurements.[3] These methods are often limited and may give rise to conflicting results as evidenced by the misassignment of structures for a number of compounds.

^{13}C NMR chemical shifts of a variety of substituted imidazoles have been reported, but there has been no attempt to use the technique to distinguish between 4- and 5-nitroimidazoles. We now report the results of such a study. The ^{13}C NMR chemical shift data[4] for various 4(5)-nitroimidazoles and 1-substituted 4- or 5-nitroimidazoles of established structure are summarised in Tables I - III. These show that the values for the ring carbon atoms are definitive for the groups of compounds and can thus be used to assign the position of the nitro group.

The chemical shifts of the unsubstituted carbon atom and those of the carbon atom bearing the nitro group are _ca_. 119 and 148 ppm for 4(5)-nitroimidazoles (Table I), and _ca_. 122 and 145 ppm for 1-substituted-4-nitroimidazoles (Table III), whereas for the 1-substituted 5-nitroimidazoles the corresponding values are _ca_. 132 and 138 ppm (Table II). The chemical shift of the ring C2 atom is also dependent on the location of the nitro substituent. Thus, in the 5-nitroimidazole series (Table II) it is at some 3-6 ppm more downfield than that of the corresponding 4-nitroimidazoles (Table III). Where the 2-substituent is a methyl group, the chemical shift of the methyl carbon atom is between 13.40-14.66 ppm in the 5-nitroimidazole series (Table II, compounds 7-14) and slightly upfield at 11.87-12.85 for the corresponding 4-nitroimidazole derivatives (Table III, compounds 17-27).

From Table III it can also be seen that where the R_1 substituent contains a carbonyl function attached directly to the ring nitrogen atom (compounds 28, 29), a slight deviation of the chemical shift associated with C5 is observed. There is a more pronounced deviation in the chemical shift of the 2-methyl carbon atom in these compounds and also in the trityl derivative (30), which may be attributed to the anisotropic effects of the carbonyl or trityl groups attached to the ring nitrogen atom.

It is also of interest to note that the close correspondence of the chemical shifts associated with C4 and C5 in compounds 1,2 and 3 (Table I) with those in compounds 16-31 (Table III) clearly indicates that the former compounds exist as the 4-nitro tautomers under the conditions employed[4] for the spectroscopic measurements.

The above results thus clearly demonstrate that ^{13}C NMR spectroscopy is the method of choice of sturcture assignment of 4- or 5-nitroimidazoles.

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9. These compounds, not previously described in the literature, were prepared by established procedures (see ref. 7) for the formation of 4-nitroimidazole derivatives, namely by reaction of 2-methyl-4(5)-nitroimidazole with the corresponding chloro-compound under

alkaline conditions. Evidence for the 4-nitroimidazole structure for these compounds was obtained from IR, UV and ^{1}H NMR studies (see ref. 7).

28: 88%; mp (toluene) 109°C. Anal. calcd. for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.21; N, 16.09. Found: C, 55.1; H, 4.09; N, 16.1.

29: 97%; mp (C_2H_5OH) 44°C. Anal. calcd. for $C_7H_9N_3O_4$: C, 42.2; H, 4.52; N, 21.1. Found: C, 42.0; H, 4.54; N, 21.4.

30: 67%; mp (toluene) 221°C. Anal. calcd. for $C_{23}H_{19}N_3O_2$: C, 74.8; H, 5.15; N, 11.4. Found: C, 74.3; H, 5.11; N, 11.2.