Applications of Proton Resonance Spectroscopy to Structural Problems. Part XXVIII.[1] Orientation of 1-Substituted 4- and 5-Nitroimidazoles

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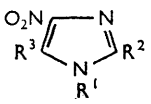
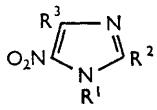
The chemical shifts of the NH-hydrogen in the conjugate acids of 1-substituted 4- and 5-nitroimidazoles depend on the relative position of the nitro-group. This method of orientation should be of general application.

1-Substituted 4- and 5-nitroimidazoles were prepared initially as potential enzyme inhibitors which might interfere with the uptake of 4(5)-aminoimidazole-5(4)-carboxyamide. Some members possess high anti-protozoal activity,[2] particularly against *Trichomonas vaginalis*. We now record the preparation and orientation of derivatives prepared by reaction of 4(5)-nitroimidazoles with chloromethyl esters or ethers at elevated temperatures in sealed tubes. These conditions were



(I)



(II)

expected [2] to give mainly 5-nitro-isomers; however, the biological activity more resembled that of 4-nitroimidazoles, which are generally less active than the 5-nitro-isomers.[2] Moreover, alkylations in the presence of potassium carbonate, conditions which usually give predominantly the 4-nitro-compound,[2] afforded the same products. The classical method [3] for assignment of structures to isomeric pairs of 1-substituted 4(5)-nitroimidazoles is reduction followed by degradation and examination of the products for *N*-alkylalanines. This is inapplicable here because the CH_2·OR or CH_2·O·COR substituents were extremely labile, and hydrolysis regenerated the unsubstituted imidazole. N.m.r. spectrosocopy was used to differentiate between structures (I) and (II), using as models isomeric pairs of 1-substituted 4- and 5-nitroimidazoles of known structure.

J_{35} in the conjugate acid of (I) should be smaller than J_{34} in the conjugate acid of (II). Unfortunately, the conjugate acids of the model compounds 1-methyl-4- and 1-methyl-5-nitroimidazole in fluorosulphonic acid gave broad peaks for the ring protons in which the N*H*-C*H* coupling constants were not resolved. Neither decoupling of the methyl group nor ^{14}N decoupling sharpened the ring CH-proton peaks. Because ^{14}N decoupling did sharpen the NH line-width, proton exchange is unlikely to be the cause of the CH broadening, which is probably due to rapid proton relaxation.

The effects of substituents on CH-proton chemical shifts in aromatic compounds is well documented; [4] for example, a nitro-group in a five-membered ring deshields CH groups α to it by 0·6—1·0 p.p.m. and CH groups β to it by 0·0—0·4 p.p.m. Similar behaviour was found for the NH-protons of the conjugate acids for isomeric pairs of 1-substituted 4- and 5-nitroimidazoles of known orientation (fluorosulphonic acid solvent). The NH-proton signals (Table) appeared as broad peaks to low-field of the other absorption; chemical shifts could be measured reproducibly to 0·1 p.p.m. Compounds with an α-nitro-group showed the NH-proton peak at τ — 2·6 to —1·8, whereas β-nitro-derivatives absorbed at τ —1·7 to —1·3. Within each range, *C*-aryl substituents displaced the NH-proton absorption to lower field and *C*-methyl to higher field, but for each isomeric pair the α-nitro NH-proton peak was at 0·8 p.p.m. to lower field than that for the β-analogue. The shifts show that the three compounds of previously unknown orientation, (I or II; R^1, = CH_2·OMe, $R^2 = R^3 = H$; τ — 2·5), (I or II; $R^1 = CH_2$·O·COMe, $R_2 = R^3 = H$; τ — 2·5), and (I or II; $R^1 = CH_2$·O·COEt, $R^2 = R^3 =$ H; τ — 2·6), are 1-substituted 4-nitroimidazoles; *i.e.*, are of structure (I).

Substituents in parent 5-nitroimidazole		*N*-Alkyl group	Chemical shifts of NH⁺ in conjugate acid (τ)		Δσ (p.p.m.)	Preparation of compounds
2-	4-		1-Alkyl 3-NH⁺	3-Alkyl 1-NH⁺		
H	3,4-$Cl_2C_6H_3$	CH_3	—1·4	—2·2	0·8	Ref. 2
H	,,	C_2H_5	—1·4	—2·2	0·8	Ref. 2
H	,,	CH_2·CH_2·OH	—1·5	—2·4	0·9	Ref. 2
H	H	CH_2·CH_2·OH	—1·6	—2·6	1·0	*a*
H	H	CH_3	—1·3	—2·1	0·8	*b*
CH_3	CH_3	CH_3	*c*	—1·8		

[a] D. R. Hoff and J. K. Bennett, U.S.P. 3,107,201/1963 (*Chem. Abs.*, 1963, **59**, 15,876). [b] W. E. Allsebrook, J. M. Gulland, and L. F. Story, *J. Chem. Soc.*, 1942, 232. [c] Peak not observed; probably obscured by solvent peak.

[1] Part XXVII, D. Cohen, P. R. Constantine, H. Heaney, A. R. Katritzky, I. T. Miller, B. M. Semple, and M. J. Sewell, preceding Paper.

[2] G. P. Ellis, C. Epstein, C. Fitzmaurice, L. Goldberg, and G. H. Lord, *J. Pharm. Pharmacol.*, 1964, **16**, 801.

[3] F. L. Pyman, *J. Chem. Soc.*, 1922, 2616.

[4] J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1966, vol. 2, pp. 782, 787, and 802.

As far as we know, the chemical shifts of NH-protons in the conjugate acids of nitrogen heteroaromatic compounds have not been used previously diagnostically, but they should be of general application.

EXPERIMENTAL

1-Methoxymethyl-4-nitroimidazole (I; $R^1 = CH_2{\cdot}OMe$, $R^2 = R^3 = H$).—4-Nitroimidazole (10 g.) and chloromethyl methyl ether (12 ml.) were heated (sealed tube) at 100° for 3 hr. The cooled residue was treated in water with an excess of sodium carbonate and extracted with chloroform. Evaporation *in vacuo* of the dried (Na_2SO_4) extracts, and repeated extraction of the residual oil with boiling ether gave, on cooling, rod-shaped crystals of the *product* (6·4 g., 46%), m. p. 66·5—67° (from benzene) (Found: C, 38·2; H, 4·6; N, 26·4. $C_5H_7N_3O_3$ requires C, 38·2; H, 4·5; N, 26·8%).

1-Acetoxymethyl-4-nitroimidazole (I; $R^1 = CH_2{\cdot}O{\cdot}COMe$, $R^2 = R^3 = H$) was prepared similarly using 4-nitroimidazole (1·7 g.) and chloromethyl acetate (4 ml.), giving rod-shaped needles of the *product* (54·0%), m. p. 83·5—84·5° (from ethyl acetate–light petroleum) (Found: C, 38·6; H, 4·0; N, 22·8. $C_6H_7N_3O_4$ requires C, 38·9; H, 3·9; N, 22·7%).

4-Nitro-1-propionyloxymethylimidazole (I; $R^1 = CH_2{\cdot}O{\cdot}COEt$, $R^2 = R^3 = H$).—This was prepared by use of chloromethyl propionate; the excess of chloromethyl ester was distilled off *in vacuo*. The *product* formed plates (24·0%), m. p. 61—62° (from ether–light petroleum) (Found: C, 41·6; H, 4·5; N, 21·5. $C_7H_9N_3O_4$ requires C, 42·2; H, 4·6; N, 21·2%).

1-(2-Hydroxyethyl)-4-nitroimidazole (I; $R^1 = CH_2{\cdot}CH_2{\cdot}OH$, $R^2 = R^3 = H$).—4-Nitroimidazole (5 g.), 2-bromoethanol (5·2 g.), and potassium carbonate (2·5 g.) were refluxed in acetone (50 ml.) for 5 hr. The solution was filtered and the filtrate and washings were treated with charcoal and fractionally precipitated with ether, to give starting material (1·2 g.) and then the *product* (1·5 g., 21%) which separated from ethanol–ether as rod-shaped crystals, m. p. 112—113° (Found: C, 38·1; H, 4·6; N, 26·5. $C_5H_7N_3O_2$ requires C, 38·2; H, 4·5; N, 26·7%).

1,2,5-Trimethyl-4-nitroimidazole (I; $R^1 = R^2 = R^3 =$ Me).—2,4-Dimethyl-5-nitroimidazole (4 g.), methyl iodide (2 ml.), and potassium carbonate (4 g.) were refluxed in acetone (100 ml.) for 3 hr. The filtrates were evaporated after charcoal treatment. The residual solid gave needles of the *product* (3 g., 68%), m. p. 170—171° (from ethanol) (Found: C, 46·1; H, 6·0; N, 26·1. $C_6H_9N_3O_2$ requires C, 46·4; H, 5·8; N, 27·1%). Nitration of 1,2,5-trimethylimidazole gave the same product.

1,2,4-Trimethyl-5-nitroimidazole (II; $R^1 = R^2 = R^3 =$ Me).—2,4-Dimethyl-5-nitroimidazole (14 g.) was heated with dimethyl sulphate (10 ml.) for 1 hr. at 100°. The product, in the minimum of water, was treated with an excess of sodium carbonate and extracted with ether. The extracts gave needles (10 g., 64%), m. p. 50—51° (from ether) (Found: C, 46·1; H, 5·8; N, 27·5%).

Spectra.—The n.m.r. spectra were recorded on a Perkin-Elmer 40 Mc./sec. spectrometer. The ^1H double resonance experiments were carried out on a Varian HA 100 spectrometer. The solutions were approximately 5% w/v, the internal reference being tetramethylammonium sulphate (τ 6·83).

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