Metabolic Ring Hydroxylation of Tinidazole† involving a Novel Nitro-group Migration: *X*-Ray Structures of Tinidazole and the NH_4^+ Salt of its Ring Hydroxylated Metabolite

Leslie F. Chasseaud,[a] Kim Henrick,[b] Ray W. Matthews,[b] Peter W. Scott,*[a] and Stuart G. Wood[a]

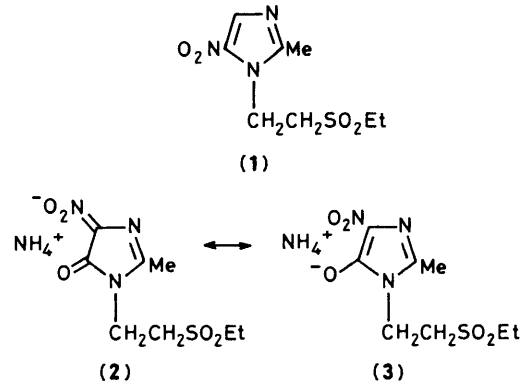
[a] *Department of Metabolism and Pharmacokinetics, Huntingdon Research Centre, Huntingdon, Cambridgeshire, PE18 6ES, U.K.*

[b] *School of Chemistry, The Polytechnic of North London, Holloway Road, London N7 8DB, U.K.*

The *X*-ray crystal structures of tinidazole and one of its major metabolites have been determined: the metabolism involves a novel nitro-group migration during ring hydroxylation.

Tinidazole, (**1**), is one of a group of nitroimidazoles which are effective antiprotozoal agents.[1] A major urinary metabolite of (**1**) is a hitherto unidentified bright-yellow compound ('metabolite 3')[2] which accounts for 14%[2] and 20%[3] of the dose of (**1**) in dog and man respectively.

Recently we have isolated 'metabolite 3' as the ammonium salt, (**2**), [u.v. absorption spectrum in aq. ammonium acetate at pH 7 : λ_{max} (ε) 370 (*ca.* 17 000), 264 (*ca.* 3 500), 225 nm (*ca.* 8 000 dm^3 mol^{-1} cm^{-1})][2] from urine after oral administration of [^{14}C]tinidazole to dogs. Unexpectedly, the structure of (**2**) has been shown by *X*-ray diffraction analysis‡ to be the 4-nitro-derivative, ammonium 1-[2-(ethylsulphonyl)ethyl]-4,5-dihydro-2-methyl-4-nitro-1*H*-imidazol-5-one.



† 1-[2-(ethylsulphonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole.

‡ *Crystal data:* (**1**), $C_8H_{13}N_3O_4S$, M = 247.27, monoclinic, space group $P2_1/n$, a = 16.873(3), b = 5.526(2), c = 11.999(2) Å, β = 97.55(3)°, U = 1109.09 Å^3, D_c = 1.480 g cm^{-3}, Z = 4, F(000) = 520, μ(Mo-K_α) = 2.26 cm^{-1}, θ range 3—25°, R = 0.0478 for 1522 data with $I>3\sigma(I)$. (**2**), $C_8H_{16}N_4O_5S$, M = 280.34, triclinic, space group $P\bar{1}$, a = 13.137(2), b = 7.519(2), c = 7.257(2) Å, α = 117.10(2), β = 97.53(2), γ = 82.39(2)°, U = 630.45 Å^3, D_c = 1.474 g cm^{-3}, Z = 2, F(000) = 296, μ(Mo-K_α) = 2.28 cm^{-1}, θ range 3—25°, R = 0.0508 for 1578 data with $I>3\sigma(I)$. Data for (**1**) and (**2**) were obtained on a Philips PW 1100 diffractometer with Mo-K_α radiation. Absorption corrections were not applied. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

In the light of this result, tinidazole itself was subjected to *X*-ray crystallographic analysis‡ and its structure confirmed as the 5-nitro-compound (**1**). This is apparently the first reported example of nitro-group migration during *in vivo* aromatic hydroxylation.

After oral administration of [^{14}C]tinidazole to dogs, compound (**2**) was isolated from the urine using reversed-phase high performance liquid chromatography in the presence of ammonium acetate buffer, followed by slow crystallization from rigorously dried methanol at 10 °C.

The *X*-ray structures of (**1**) and (**2**) are shown in Figures 1 and 2 respectively. Formulation of the nitro-group in (**2**) as $-C{=}NO_2^-$ is supported by comparison of bond lengths with those in nitroimidazole compounds,[4] including (**1**), containing

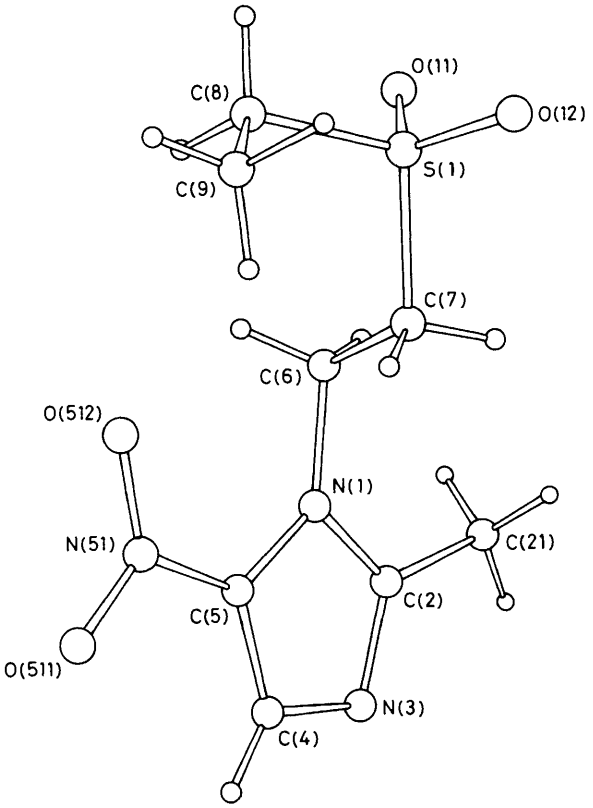


Figure 1. The structure of 1-[2-(ethylsulphonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole (**1**). Important bond lengths are: N(1)–C(2) 1.357(4), C(2)–N(3) 1.335(4), N(3)–C(4) 1.354(5), C(4)–C(5) 1.362(4), C(5)–N(1) 1.388(4), C(5)–N(51) 1.412(4), N(51)–O(511) 1.229(4), and N(51)–O(512) 1.229(4) Å.

–C–NO_2 groups, and with those in a compound[5] incorporating both types of nitro-group. The pattern of bond lengths in the imidazole ring is also consistent[6] with this formulation for (**2**), although the C–O bond length is slightly longer than previously found for keto-imidazoline rings,[6,7] probably due to hydrogen bonding to NH_4^+. However, it is possible that in solution the compound exists as a mixture of forms, (**2**) and (**3**), as has been suggested for ring-hydroxylated nitrofurantoin[8] and a hydroxylated metabolite of ipronidazole.[9]

Received, 10th January 1984; Com. 034

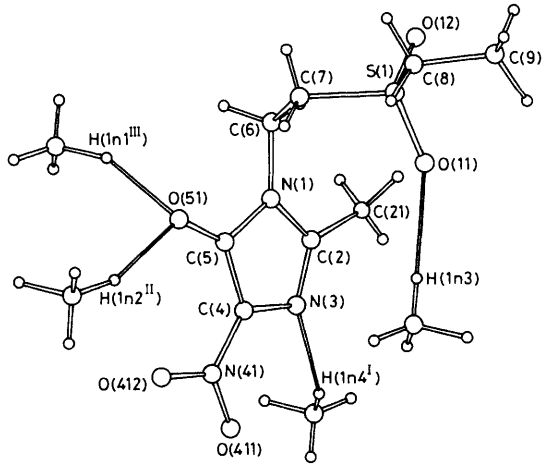


Figure 2. The structure of ammonium 1-[2-(ethylsulphonyl)ethyl]-4,5-dihydro-2-methyl-4-nitro-1*H*-imidazol-5-one (**2**). Important bond lengths are: N(1)–C(2) 1.390(4), C(2)–N(3) 1.299(5), N(3)–C(4) 1.388(4), C(4)–C(5) 1.427(5), C(5)–N(1) 1.394(5), C(4)–N(41) 1.364(5), N(41)–O(411) 1.250(4), N(41)–O(412) 1.265(4), and C(5)–O(51) 1.252(4) Å. The anion in (**2**) forms strong intermolecular hydrogen bonds with the protons of the ammonium ion, with O(11) · · · H(1n3) 2.15, N(3) · · · H(1n4^{I}) 2.19, O(51) · · · H(1n2^{II}) 2.00, O(51) · · · H(1n1^{III}) 1.88 Å; where symmetry transformation (I) = $1-x,-1-y,-z$; (II) = $1-x,-y,1-z$; (III) = $x,1+y,z$.

References

1 C. E. Nord, *J. Antimicrob. Chemother.*, 1982, **10**, Suppl, A, 35.
2 A. M. Monro, D. Rycroft, and B. A. Wood, *Xenobiotica*, 1973, **3**, 801; B. A. Wood, personal communication.
3 S. G. Wood, unpublished results.
4 A. Kalman, F. van Meurs, and J. Toth, *Cryst. Struct. Commun.*, 1980, **9**, 709; N. M. Blaton, O. M. Peeters, and C. J. DeRanter, *Acta Crystallogr., Sect. B*, 1979, **35**, 2465; G. Germain, J. P. Declercq, M. van Meerssche, and M. H. J. Koch, *ibid.*, 1977, **33**, 2269.
5 G. G. Messmer and G. J. Palenik, *J. Chem. Soc., Chem. Commun.*, 1969, 470.
6 B. Tinant, G. Germain, J. P. Declercq, and M. van Meerssche, *Cryst. Struct. Commun.*, 1980, **9**, 671.
7 G. Glidewell, H. D. Holden, and D. C. Liles, *J. Mol. Struct.*, 1980, **66**, 325; M. Acheson, J. D. Wallis, and D. J. Watkins, *Acta Crystallogr., Sect. B*, 1980, **36**, 3179.
8 J. Olivard, G. M. Rose, G. M. Klein, and J. P. Heotis, *J. Med. Chem.*, 1976, **19**, 729.
9 G. Weiss, N. Rose, P. Duke, and T. H. Williams, *Xenobiotica*, 1981, **11**, 207.