Biochemical Pharmacology, Vol. 34, No. 3, pp. 457–458, 1985.
Printed in Great Britain.

0006-2952/85 $3.00 + 0.00

A Novel Metabolite of Tinidazole involving Nitro-group migration

P. W. Scott, S. G. Wood and L. F. Chasseaud
Department of Metabolism and Pharmacokinetics
Huntingdon Research Centre,
Huntingdon, Cambs. PE18 6ES,
U.K.

R. W. Matthews and K. Henrick
School of Chemistry,
The Polytechnic of North London,
Holloway Road,
London, N7 8DB,
U.K.

Introduction

Tinidazole (1) is one of a group of nitroimidazoles which are effective antiprotozoal agents (Nord, 1982). A major urinary metabolite of (1) is a hitherto unidentified bright-yellow compound 'metabolite 3' which accounts for 14% (Wood, Rycroft and Monro, 1973) and 20% (unpublished data) of the dose of tinidazole in dog and man respectively. Recently we have isolated sufficient metabolite 3 to permit unequivocal identification of its structure.

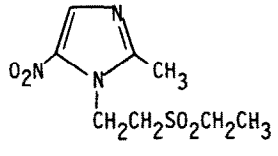
Experimental

After oral administration of ^{14}C-tinidazole to dogs, metabolite 3 was isolated from the urine using two reversed phase high-performance liquid chromatography systems. After an initial 'clean-up', metabolite 3 was separated from the glucuronic acid conjugate of hydroxymethyltinidazole using a semi-preparative column prepacked with Spherisorb 10 O.D.S. and eluted with 0.1M ammonium acetate-methanol (95 : 5 v/v). Metabolite 3 was finally isolated by slow crystallisation from rigorously dried methanol at 10°C.

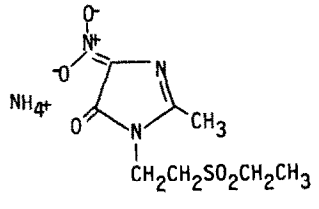
Results

The ultra-violet spectrum (λmax. 370 nm, ε 17000) and ^{1}H-nmr spectrum in MeOH-d4 [δ 1.33 (t, J=7.5 Hz) 3H(a); δ 2.30 (s) 3H (b); δ 3.09 (q, J=7.5 Hz) 2H (c); δ 3.51 (t, J=6.3 Hz) 2H (d); δ 4.13 (t, J=6.3 Hz) 2H (e)] of metabolite 3 indicated a ring-hydroxylated tinidazole structure. This was supported by the FAB mass spectrum (m/e 262) and the elemental analysis (Found (mean) C, 34.6; H, 5.9; N, 20.3; S, 11.8%. Calculated for $C_8H_{12}N_3O_5S.NH_4$: C, 34.3 H, 5.7; N, 20.0; S, 11.4%) which suggested that metabolite 3 had been isolated as the ammonium salt of ring-hydroxylated tinidazole.

The structure of metabolite 3 was shown by X-ray diffraction analysis to be the ammonium salt of the 4-nitroimidazolin-5-one (2a). In the light of this unexpected result, tinidazole itself was also subjected to X-ray crystallographic analysis and its structure confirmed as the expected 5-nitro-compound (1).

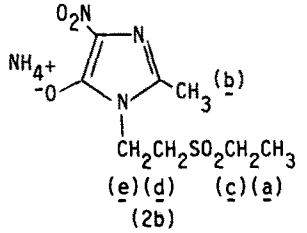


Tinidazole (1)



(2a)

Metabolite 3



(2b)

Discussion

Formulation of the nitro-group in metabolite 3 as $C{=}NO_2^-$ is supported by comparison of the bond lengths for metabolite 3 with those in a range of nitromidazole compounds, including tinidazole, and with those in a compound incorporating both types of nitro-group (Messmer and Palenik, 1969).

However, it is possible that in solution the compound exists as a resonance hybrid of forms (2a) and (2b) has been suggested for ring-hydroxylated nitrofurantoin (Olivard et al., 1976) and a hydroxylated metabolite of ipronidazole (Weiss et al., 1981). The mechanism of formation of this unusual metabolite presumably involves a rearrangement perhaps analogous to the "NIH shift" (Jerina and Daly, 1974 in which intramolecular migration of the 5-nitro-group to the 4-position is preceded by epoxidation of the 4, 5-double bond.

References

D. M. Jerina and J. M. Daly (1974) Arene oxides: a new aspect of drug metabolism. Science, 185, 573

G. G. Messmer and G. J. Palenik (1969) The crystal structure of a meisenheimer complex: the potassium methoxide adduct of 4-methoxy-5, 7-dinitrobenzofurazan. J. Chem. Soc., Chem. Commun., 470

C. E. Nord (1982) Microbiological properties of tinidazole: spectrum, activity and ecological considerations. J. Antimicrob. Chemother. 10, Suppl. A. 35

J. Olivard, G. M. Rose, G. M. Klein and J. P. Heotis (1976) Metabolic and photochemical hydroxylation of 5-nitro-2-furancarboxaldehyde derivatives. J. Med. Chem. 19, 729

G. Weiss, N. Rose, P. Duke and T. H. Williams (1981) A major rat faecal metabolite of ipronidazole. Xenobiotica 11, 207

B. A. Wood, J. K. Faulkner and A. M. Monro (1982) The Pharmacokinetics, metabolism and tissue distribution of tinidazole. J. Antimicrob. Chemother. 10, Suppl. A,43

B. A. Wood, D. Rycroft and A. M. Monro (1973) The metabolism of tinidazole in the rat and dog. Xenobiotica 3, 801