THE METABOLISM OF THIONICOTINAMIDE IN THE RAT

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SUMMARY

The metabolism of the thioamide, thionicotinamide, in the male Wistar rat is described. Thionicotinamide was shown to be metabolised to inorganic sulphate, thionicotinamide S-oxide and also N^1-methylnicotinamide, which arises from N-methylation of nicotinamide via desulphuration of the parent thioamide. At 24 hours from dosing about 35% of the dose had been excreted as inorganic sulphate and 20.5% as the S-oxide metabolite. Three metabolites, detected by their fluorescence under UV light, have not been positively identified but are postulated to be pyridones, resulting from ring oxidation, by analogy with other thioamides. S-Oxidation is an important metabolic pathway as it may give rise to toxic intermediates.

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INTRODUCTION

The thioamide moiety is found in drugs, chemicals and agricultural agents, and exposure to these agents may result in a variety of toxic responses /1,2/. A number of therapeutically useful drugs, such as the tuberculostatic ethionamide, contain a thioamide group, but have limited use owing to side effects which include hepatotoxicity /3,4/.

It seems that, in most cases examined, the toxic response of thioamide-containing compounds is related to the formation of oxidative metabolites /5,6/ involving two sequential S-oxidations resulting in a thioamide S-oxide and a thioamide S,S-dioxide /1,7,8/. The first oxidation is considered to be a detoxification pathway leading to the formation of the relatively stable thioamide S-oxide. However, the S,S-dioxide once formed is extremely reactive chemically; it cannot be isolated and must be generated and used *in situ* /1/. It is the S,S-dioxide metabolites which have been implicated as being responsible for the toxicity of thioamides /8-10/.

Desulphuration, with the formation of the corresponding amide, is also known to be an important metabolic route for thioamides /1,10/; the mechanisms involved are not clear, but are again believed to involve oxidative processes /11-13/.

Thionicotinamide has not been previously studied; the compound was used as a model to investigate the relative importance of the different oxidative pathways in thioamide metabolism, and to determine the fate of the thioamide group. As thionicotinamide is the thio-analogue of nicotinamide, which can be synthesised endogenously from tryptophan, evidence was sought for entry into normal metabolic pathways.

MATERIALS AND METHODS

Materials and General Methods

Thionicotinamide, N^1-methylnicotinamide, nicotinic acid and nicotinamide N-oxide were obtained from Sigma Chemicals (Poole, Dorset). 1-Methyl-2-pyridone-5-carboxamide was a gift from Dr. D.A. Bender (Middlesex Hospital Medical School, London).

Male Wistar rats (250 ± 20 g) were used throughout the study. Thionicotinamide was administered orally (100 mg/kg body weight) as a fine suspension in 1 ml 3% methylcellulose (Collagel, Eli Lilly

and Co., Ltd., Herts.). Animals were housed in glass metabolism cages (Metabowls, Jencons Ltd., Herts.) facilitating the separate collection of faeces and urine over dry ice. Faeces and urine were collected at 24 hour intervals for 3 days. Animals had free access to food and water.

[^{35}S]-Thionicotinamide (specific activity: 0.19 μCi/mg; chemical purity: 98%) was synthesised by the method of Pilkington and Waring /14/ for the synthesis of [^{35}S]-penicillamine. Thionicotinamide S-oxide was synthesised by the method of Porter and Neal /15/ for the formation of thioacetamide S-oxide; it was purified by thin layer chromatography (see below) and subjected to mass spectral analysis.

Chromatography

Thin layer chromatography (TLC) was carried out on Silica gel plates (0.25 mm) using chloroform: methanol (3:1, v/v) as the solvent system. The Dragendorf reagent /16/ was employed for detection of thioamide metabolites.

Two high performance liquid chromatographic (HPLC) techniques were employed.

HPLC Method 1 was employed as previously described /17/ to separate thionicotinamide and thionicotinamide S-oxide. HPLC Method 2 was a modification of the method used by McKee *et al.* /18/ employing a linear ion-pair mobile phase gradient to separate nicotinamide, nicotinic acid, N^1-methylnicotinamide, 1-methyl-2-pyridone-5-carboxamide and nicotinamide N-oxide. A Spherisorb 50DS C18 column (250 mm x 4.6 mm ID) was used as the stationary phase (HPLC Technology Ltd., Macclesfield, Cheshire). Two ion-pairing reagents were used: 1-pentanesulfinic acid sodium salt (PSA) and tetramethylammonium chloride (TMA). Solvent A consisted of 10 mM concentrations of PSA and TMA and 10 mM KH_2PO_4 in deionised water. Solvent B consisted of 100 ml deionised water containing 10 mM PSA and 10 mM TMA plus 900 ml acetonitrile. A linear ion-pair mobile phase gradient was programmed from 0% to 10% Solvent B in 10 minutes. The column was then regenerated and equilibrated for 5 minutes with an A:B ratio 100:0. Gradient systems elutions were carried out using an ACS 350/04 Pump, ACS 351/04 Gradient Controller, and an ACS 750/12 UV detector with a continual helium degassing unit (ACS, Macclesfield, Cheshire).

Isolation and analysis of metabolites

Urinary metabolites of thionicotinamide were detected and quantified by TLC and HPLC using co-chromatography with authentic standards dissolved in control urine from animals dosed with only methyl cellulose.

All urine samples were then concentrated by lyophilization, extracted with methanol and examined by TLC, using 50-100 μl of the extract. Detection of metabolites was achieved by spraying thin-layer chromatograms with the Dragendorf reagent. The thin-layer chromatograms were also viewed under UV light (366 nm) to enable the detection of fluorescent metabolites; R_f values for authentic thionicotinamide, nicotinamide and their metabolites are shown in Table 1a.

The isolation of unknown metabolites was achieved by eluting the relevant areas with either methanol or water from thin-layer chromatograms. The eluates were filtered (Whatman Paper No. 1) and dried under reduced pressure. The extract was dissolved in a small volume of methanol or water and analysed by electron impact mass spectrometry carried out on a Kratos D580 instrument with samples loaded at room temperature in a field of 6KV.

Metabolite detection was verified by HPLC; samples of neat urine (1-10 μl), from dosed animals, were used, with authentic standards dissolved in control urine for co-chromatography. The retention times of thionicotinamide, nicotinamide and their metabolites are shown in Table 1b. Using HPLC Method 1 there was a linear correlation between peak area and thioamide concentration enabling the construction of standard curves for thionicotinamide and thionicotinamide S-oxide quantification. The use of a Trio-LA500 Trivector Chromatography Integrator Package (Trivector Systems Inc. Ltd., Sandy, Bedfordshire) was employed to analyse results when using HPLC Method 2. The identity of the peaks was verified by spiking the sample with the appropriate standard and observing the resulting increase in peak area.

Quantification of urinary inorganic sulphate as [^{35}S]-SO_4^{2-}, after administration of [^{35}S]-thionicotinamide was based on the method of Pushpendran /19/. Liquid scintillation counting was carried out using Optiphase Hisafe 3 (Fisons) on the scintillant.

Faecal samples from rats dosed with [^{35}S]-thionicotinamide were lyophilised and ground to a homogenous powder. Samples (50 mg) were solubilised in 2 ml Soluene-350 at 60° for 16 h. Hydrogen

peroxide (30%) was then added dropwise (4 drops) to decolourise the solutions; 1 ml aliquots were analysed by liquid scintillation counting. Faecal samples were also extracted with methanol after lyophilisation. This solution was filtered, evaporated and used for chromatography.

RESULTS

Using TLC separation, and detection by the Dragendorf reagent and fluorescence under UV light, six metabolites were detected as shown in Table 1a. Co-chromatography with authentic standards indicated that Metabolite 1 was thionicotinamide (R_f = 0.88), that Metabolite 2 was thionicotinamide S-oxide (R_f = 0.67), and that Metabolite 3 was N^1-methylnicotinamide. In order to verify these results Metabolites 2 and 3 were eluted from the plates, purified and analysed by mass spectometry.

TABLE 1a

Thin-layer chromatographic analysis of thionicotinamide and metabolic products in the male Wistar rat

Metabolite	R_f value	Identification
thionicotinamide*	0.88	-
thionicotinamide S-oxide*	0.67	-
N^1-methylnicotinamide	0.05	-
Metabolite 1*	0.88	thionicotinamide
Metabolite 2*	0.67	thionicotinamide S-oxide
Metabolite 3*	0.05	N^1-methylnicotinamide
Metabolite 4^+	0.17	unknown
Metabolite 5^+	0.74	unknown
Metabolite 6^+	0.82	unknown

All metabolites were detected either by Dragendorf reagent* or by their fluorescence under UV light (366 nm^+). Solvent system: Chloroform: methanol, 3:1 (v/v).

TABLE 1b

Retention times for thionicotinamide, nicotinamide and their metabolites by HPLC

	Retention times (minutes)	
Metabolite	HPLC Method 1	HPLC Method 2
Thionicotinamide	5.3	–
Thionicotinamide S-oxide	4.6	–
Nicotinamide	–	8.57
Nicotinic acid	–	3.35
N^1-Methylnicotinamide	–	5.15
1-Methyl-2-pyridone-5-carboxamide	–	7.82
Nicotinamide N-oxide	–	4.56

Figures 1a and 1b show the mass spectra which were obtained from authentic thionicotinamide S-oxide and Metabolite 2 respectively. The authentic thionicotinamide S-oxide gave a top mass peak at m/e 154 ($M=C_6H_6N_2SO$; mol.wt. = 154.2). A major fragmentation ion was observed at m/e 138 which is indicative of loss of oxygen from the molecule. Another fragmentation ion was observed at m/e 122 which may relate to detachment of the oxygen and amide group from the parent ion. A very similar fragmentation pattern was obtained with Metabolite 2 although the largest peak was not at m/e 154.

Figures 2a and 2b show the mass spectra which were obtained from authentic N^1-methylnicotinamide chloride and Metabolite 2 respectively. Both spectra have top mass peaks at m/e 137 ($M=C_7H_9N_2O_3$; mol.wt. = 137.2) and also show very similar fragmentation patterns.

The identity of thionicotinamide and thionicotinamide S-oxide was further verified by HPLC and the excretion of these two compounds was similarly quantified (Table 2). Metabolites 1 and 2 were eluted with exactly the same retention times as authentic thionicotinamide (5.3 minutes) and thionicotinamide S-oxide (4.6 minutes) respectively. As shown in Table 2 at 24 hours after dosing,

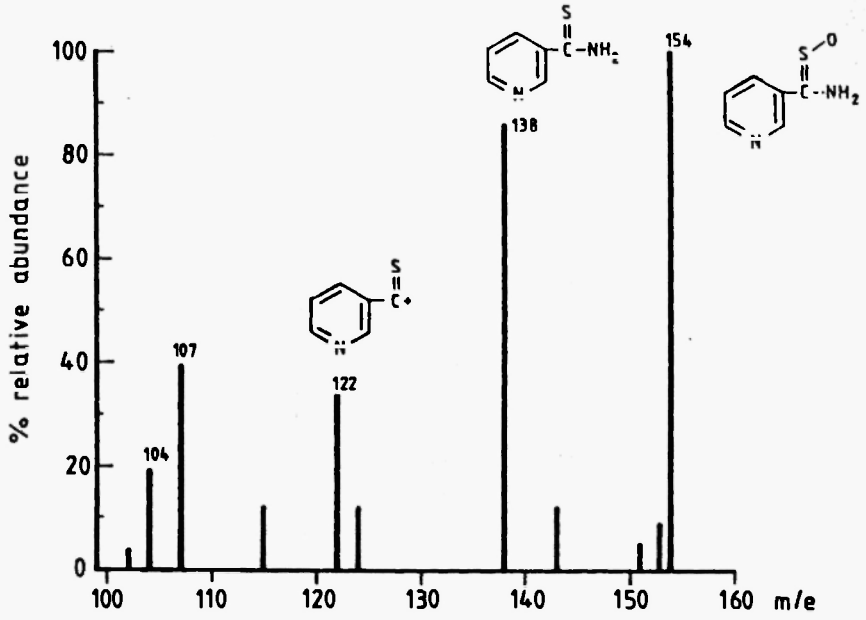

Fig. 1a: Mass spectra of authentic thionicotinamide S-oxide

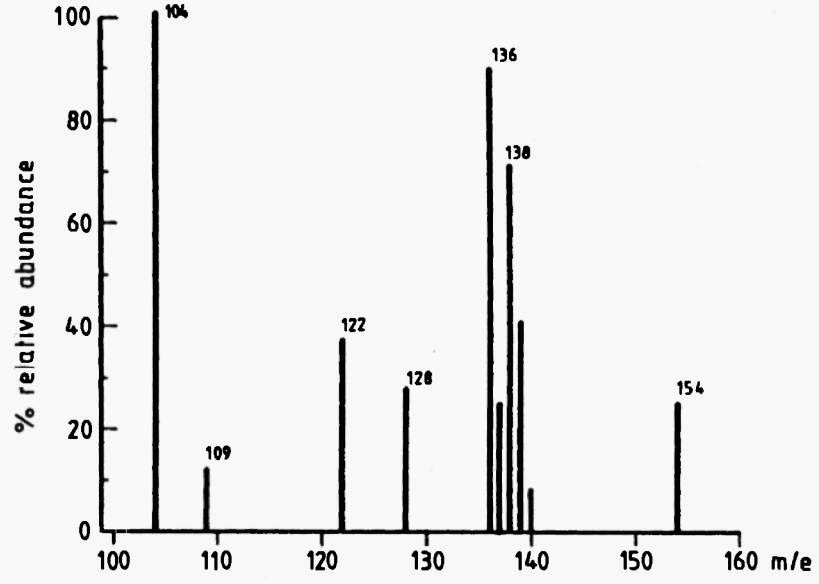

Fig. 1b: Mass spectra of Metabolite 2

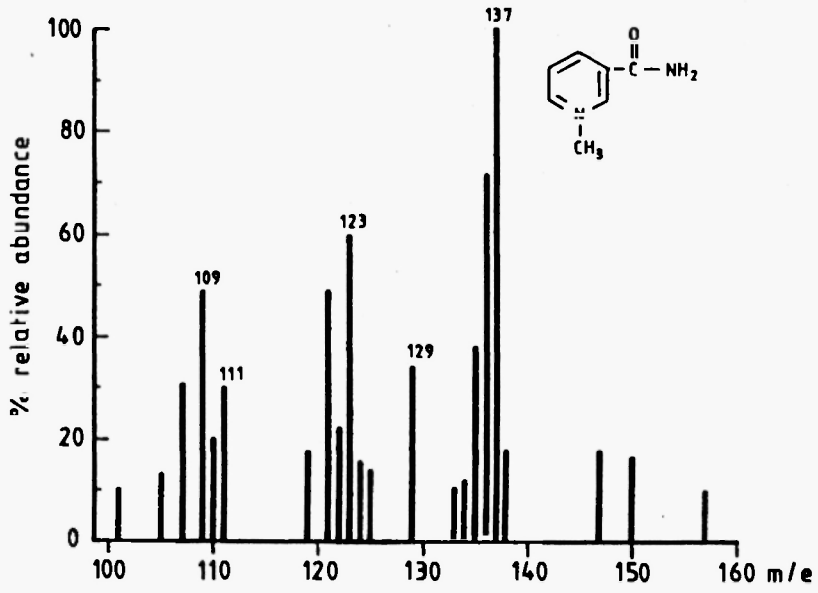

Fig 2a: Mass spectra of authentic N^1-methylnicotinamide

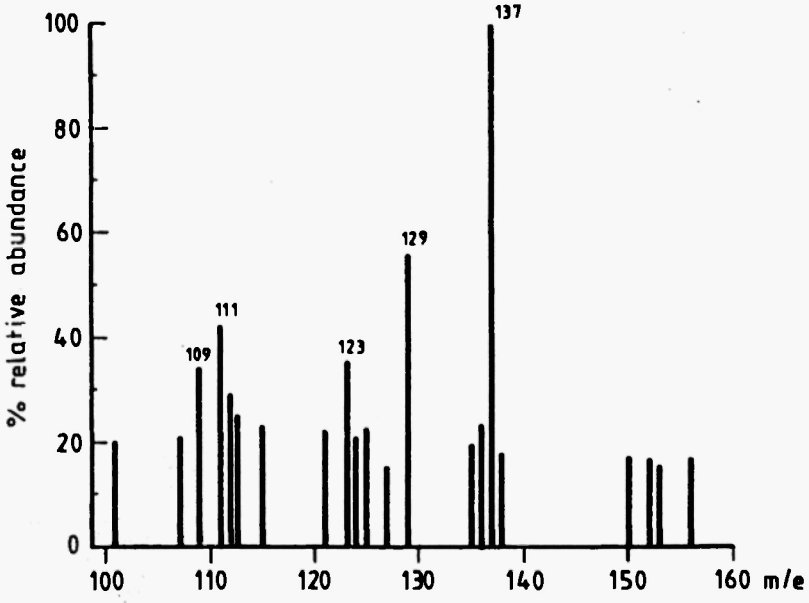

Fig. 2b: Mass spectra of Metabolite 3

TABLE 2

The excretion of thionicotinamide, thionicotinamide S-oxide and inorganic sulphate in the male Wistar rat after oral administration with thionicotinamide (n=6 ± standard deviation)

Time after dosing (hours)	Urinary Inorganic Sulphate[+] % dose	Urinary Thionicotinamide* μ moles	% dose	Urinary Thionicotinamide S-oxide* μ moles	% dose	Faecal Excretion[#] % dose
24	35.4 ± 5.8	7.8 ± 2.0	2.3 ± 0.5	71.1 ± 21.6	20.5 ± 6.8	5.5 ± 1.1
48	4.6 ± 2.4	5.2 ± 3.5	1.3 ± 0.8	3.9 ± 1.3	1.1 ± 0.3	2.2 ± 0.2
72	0.7 ± 0.1	0.36 ± 0.1	0.7 ± 0.1	3.1 ± 0.7	0.4 ± 0.04	1.0 ± 0.8

[+] determined by excretion of [^{35}S]-sulphate after dosing with [^{35}S]-thionicotinamide (3.0 μCi/kg body weight).
* determined by HPLC (method 1).
[#] determined by measurement of [^{35}S]-radioactivity.

TABLE 3

The excretion of nicotinamide and its metabolites in the male Wistar rat before and after oral administration of thionicotinamide (n=4 ± standard deviation)

	μmole excretion				
Time (hours)	Nicamide	Nic acid	N^1-MN	2 PY	Nic Noxide
Control 0-24	47.6 ± 2.0	73.7 ± 47.3	16.8 ± 9.1	2.5 ± 0.9	3.2 ± 0.2
Control 24-28	36.3 ± 9.7	64.4 ± 16.4	23.1 ± 4.6	2.71 ± 1.06	2.7 ± 0.8
Dose 0-24	26.4 ± 13.0	47.2 ± 27.3	61.7 ± 28.8*	3.0 ± 1.2	4.7 ± 2.2
Dose 24-48	33.8 ± 17.8	30.0 ± 20.6	36.1 ± 7.7	2.6 ± 1.6	1.5 ± 0.4
Dose 48-72	29.9 ± 14.7	56.4 ± 40.0	29.6 ± 8.6	1.2 ± 1.4	5.5 ± 4.0

*Increase compared to control value, $p < 0.05$ (Student's t-test).
Abbreviations: Nicotinamide (Nicamide), Nicotinic acid (Nic acid), N^1-Methylnicotinamide (N^1-MN); 1-methyl-2-pyridone-5-carboxamide (2PY); Nicotinamide N-oxide (Nic Noxide). Analysis by HPLC method 2.

only 2.3% ± 0.55% had been excreted as the parent thionicotinamide whereas 20.5% ± 6.8% had been excreted as thionicotinamide S-oxide.

The excretion of N^1-methylnicotinamide was determined by HPLC (Method 2). This method also allowed simultaneous determination of nicotinamide, nicotinic acid, 1-methyl-2-pyridone-5-carboxamide and nicotinamide N-oxide. The only significant increase in excretion ($p<0.05$) was shown by N^1-methylnicotinamide at 24 hours after dosing with thionicotinamide (Table 3).

Three metabolites were also detected by TLC but these metabolites (4, 5 and 6) have not been positively identified. All fluoresced at 366 nm; however, none co-chromatographed with standard 1-methyl-2-pyridine-5-carboxamide. Quantification using this standard suggested that the total excretion of all three compounds was about 10% of the administered dose.

The excretion of inorganic sulphate, as [^{35}S]-sulphate, was also determined in animals dosed with [^{35}S]-thionicotinamide (3 μCi/kg body weight). As shown in Table 2, 35.44 ± 5.8% of the dose was eliminated in this form.

Faecal excretion of radioactivity after dosage with [^{35}S]-thionicotinamide was 8.7% after 72 h. Chromatography revealed that this was largely due to the parent compound, presumably unabsorbed from the gut.

DISCUSSION

This study has shown that inorganic sulphate accounts for about 35% of a dose of thionicotinamide, representing quantitatively the most important urinary metabolite. S-Oxidation and desulphuration are important metabolic pathways for thionicotinamide as has also been demonstrated for thioacetamide /20/ and ethionamide /21,22/.

Thioamide sulphur is known to be susceptible to S-oxidation *via* oxidant electrophilic attack /23/. This initial oxidation is considered to be the first step in the formation of an S,S-dioxide, or sulphene metabolite, postulated as causing thioamide induced toxicity /9,23,24/. Thioamide S-oxides have also been reported for thioacetamide /5,25/ and thiobenzamide /8,26/.

The desulphuration of thionicotinamide results in the oxo-analogue, nicotinamide. When nicotinamide is administered the

major urinary metabolite is N^1-methylnicotinamide /27-29/; this compound was identified as a metabolite of thionicotinamide by TLC and mass spectrometry. Urinary levels of N^1-methylnicotinamide excretion were also shown to increase after thionicotinamide dosing (Table 3), presumably from desulphuration followed by N-methylation.

Urinary levels of the other metabolites of nicotinamide, namely 1-methyl-2-pyridone-5-carboxamide /27/ and nicotinamide N-oxide /27,30/, were shown not to increase significantly after thionicotinamide administration. However, excretion of these metabolites increases only after high doses of nicotinamide /27,31/; they would not therefore be detected as metabolites of thionicotinamide. Other workers /32/ have shown that after nicotinamide administration to rats, the major metabolite is the N^1-methyl derivative, with minimal amounts of the 1-methyl-2-pyridone carboxamide.

Three metabolites which have not been positively identified were detected by their fluorescence under UV light (366 nm). Studies with ethionamide have also resulted in the detection of similar metabolites /21,33,34/, and it has been postulated that these compounds can be identified from their fluorescence as pyridones resulting from ring oxidation. Prema and Gopinathan /34/ have identified both thio and desulphurated pyridone derivatives of ethionamide.

A number of mechanisms have been suggested for desulphuration /8,9,13,35,36/. Oxathiiranes (with a three-membered carbon-oxygen-sulphur ring system) have been postulated as intermediates in the metabolism of sulphines /35/, carbon disulphide /37/ and phosphorothionates /38/, and as one of the mechanisms for the desulphuration of thioacetamide /13/. Experiments investigating the incorporation of ^{18}O suggest that this pathway may account for between 25-33% of the reaction /13/. In contrast, however, other workers have reported that oxathiiranes do not contribute to thioamide desulphuration /1,8,9/. Evidence from studies investigating the formation of amides from thioamides and thioamide S-oxides /8,9/, and also thermal considerations /1/ (Cashman JR, personal communication 1990), suggest that thioamide desulphuration proceeds by way of the thioamide S,S-dioxide intermediate rather than an oxathiirane. It has also been reported that thioamide desulphuration can be mediated by superoxide anions at room temperature, thionicotinamide being converted to nicotinamide with a yield of 71% /36/.

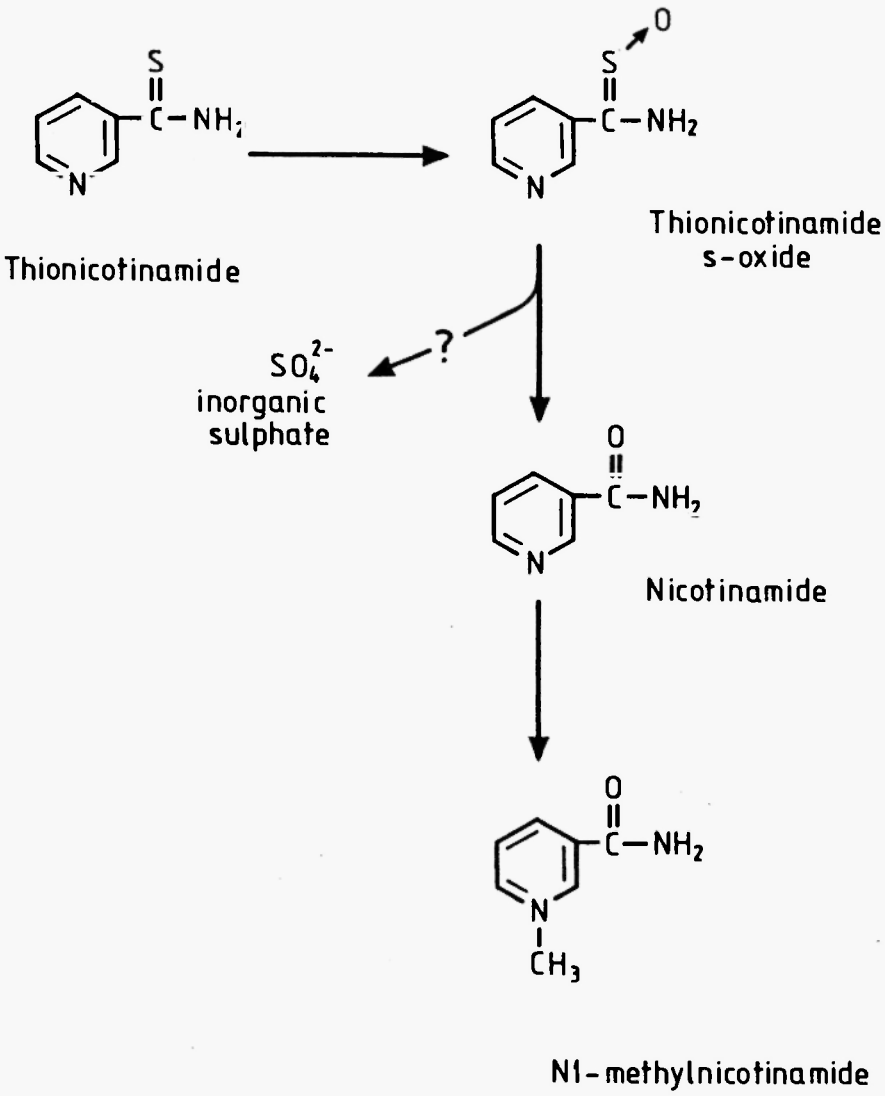

Fig. 3: Proposed metabolism of thionicotinamide by the Wistar rat

The proposed metabolism of thionicotinamide is shown in Figure 3. The results presented clearly show that S-oxidation and desulphuration are major pathways of metabolism for thionicotinamide; S-oxidation may be particularly important in leading to the formation of toxic intermediates /39/.

ACKNOWLEDGEMENTS

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REFERENCES

1. Cashman JR. Thioamides. In: Damani LA, ed., Sulphur-containing Drugs and Related Organic Compounds (Volume 1, Part B). Chichester: Ellis Horwood Ltd., 1989; 35-48.
2. Neal RA, Halpert J. Toxicology of thiono-sulphur compounds. Ann Rev Pharmacol Toxicol 1982; 22: 321-339.
3. Waring RH, Mitchell SC, Ruse MJ. Antituberculosis drugs: ethionamide and related compounds. In: Damani LA, ed., Sulphur-containing Drugs and Related Organic Compounds (Volume 3, Part B). Chichester: Ellis Horwood Ltd., 1989; 165-180.
4. Cartel JL, Millan J, Guelpa-Lauras CC, Grosset JH. Hepatitis in leprosy patients treated by a daily combination of dapsone, rifampicin, and a thioamide. Int J Leprosy 1983; 51(4): 461-465.
5. Chieli E, Malvaldi G. Role of the microsomal FAD-containing monooxygenase in the liver toxicity of thioacetamide S-oxide. Toxicology 1984; 31: 41-52.
6. Hanzlik RP, Cashman JR, Traiger GJ. Relative hepatotoxicity of substituted thiobenzamide and thiobenzamide S-oxide in the rat. Tox Appl Pharmacol 1980; 55: 260-272.
7. Penny DA, Gottschalk DW, Hanzlik RP, Traiger GJ. The role of metabolism in N-methyl thiobenzamide-induced pneumotoxicity. Tox Appl Pharmacol 1985; 78: 323-331.
8. Hanzlik RP, Cashman JR. Microsomal metabolism of thiobenzamide and thiobenzamide S-oxide. Drug Metab Disp 1983; 11(3): 201-205.
9. Dyroff MC, Neal RA. Studies on the mechanism of metabolism of thioacetamide S-oxide by rat liver microsomes. Mol Pharmacol 1983; 23: 219-227.
10. Neal RA. Microsomal metabolismn of thiono-sulfur compounds: mechanisms and toxicological significance. In: Hodgson E, Bend JR, Philpot RM, eds., Reviews in Biochemical Toxicology (Volume 2). New York: North Holland, 1980; 131-171.
11. Ziegler DM. S-Oxygenases, I: chemistry and biochemistry. In: Damani LA,

ed., Sulphur-containing Drugs and Related Organic Compounds (Volume 2, Part A). Chichester: Ellis Horwood Ltd., 1989; 53-66.
12. Poulson LL. Organic sulfur substrates for the microsomal flavin-containing monooxygenases. Rev Biochem Toxicol 1981; 3: 33-49.
13. Hillhouse JH, Blair IA, Field L. Thiono compounds. 7. Oxidation of thioamides in relation to adverse biological effects. Phosphorus and Sulfur 1986; 26: 169-184.
14. Pilkington AE, Waring RH. D-penicillamine metabolism: in vitro studies using DA strain rat livers. Med Sci Res 1987; 15: 213-214.
15. Porter WR, Neal RA. Metabolism of thioacetamide and thioacetamide S-oxide by rat liver microsomes. Drug Metab Disp 1978; 6: 379-388.
16. Dawson RMC, Elliot DC, Elliot WH, Jones KM. Data for Biochemical Research. Oxford: Clarendon Press, 1986.
17. Ruse MJ, Waring RH. HPLC analysis of thioamides and their sulphoxides. Med Sci Res 1990; 18: 53-54.
18. McKee RW, Kang-Lee YA, Panaqua M, Swendseid ME. Determination of nicotinamide and metabolic products in urine by high-performance liquid chromatography. J Chromatogr 1982; 230: 309-317.
19. Pushpendran CK, Devisagavam TPA, Chintalwar GJ, Banerji A, Eapen J. The metabolic fate of ^{35}S-diallyl-disulphide in mice. Experientia 1980; 36: 1000-1001.
20. Porter WR, Gudzinowicz MJ, Neal RA. Thioacetamide-induced hepatic necrosis, II: pharmacokinetics of thioacetamide and thioacetamide S-oxide. J Pharm Exp Therapeutics 1979; 208(3): 386-391.
21. Johnston JP, Kane PO, Kibby MR. The metabolism of ethionamide and its sulphoxide. J Pharm Pharmacol 1967; 19: 1-9.
22. Waring RH, Armitage M, Mitchell SC. Sulphoxidation in the neonatal guinea pig. Biochem Soc Trans 1978; 6: 91-93.
23. Cashman JR, Hanzlik RP. Oxidation and other reactions of thiobenzamide derivatives of relevance to their hepatotoxicity. J Org Chem 1982; 47: 4645-4650.
24. Hanzlik RP, Cashman JR. Microsomal metabolism of thiobenzamide and thiobenzamide S-oxide. Drug Metabol Disp 1983; 11: 201-205.
25. Rees KR, Rowland GF, Varcoe JS. The metabolism of tritiated thioacetamide in the rat. Int J Cancer 1966; 1: 197-203.
26. Chieli E, Malvaldi G, Segnini D. The hepatotoxicity of thiobenzamide S-oxide. Toxicol Lett 1980; 7: 175-180.
27. McCreanor GM, Bender DA. The metabolism of high intakes of tryptophan, nicotinamide and nicotinic acid in the rat. Br J Nutr 1986; 56: 577-586.
28. Shibata K, Matsuo H. Inhibition of N1-methylnicotinamide oxidase activity by a large nicotinamide injection into rats. Agric Biol Chem 1989; 53(8): 2031-2036.
29. Shibata K, Matsuo H. Inhibition of N1-methylnicotinamide oxidase activity by a large amount of N1-methylnicotinamide injected into rats. Agric Biol Chem 1989; 53(9): 2393-2397.
30. Mrochek JE, Jolley RL, Young DS, Turner WJ. Metabolic response of humans to ingestion of nicotinic acid and nicotinamide. Clinical Chem 1976; 22: 1821-1827.

31. Shibata K, Matsuo H. Changes in the ratio of N1-methyl-2-pyridone-5-carboxamide to N1-methyl-4-pyridone-3-carboxamide excretion following a large amount of N1-methylnicotinamide injection in rats. Agric Biol Chem 1989; 53: 1161-1162.
32. Young KL, McKee RW, Wright SM, Swendseid ME, Jenden DJ, Jape RS. Metabolism of nicotinamide in the rat. J Nutr 1983; 113: 215-221.
33. Yamamoto M. Fate of 2-ethyl-thioisonicotinamide (1314TH) in human beings (report I). Jpn J Ches Dis 1962; 6: 1036-1041.
34. Prema K, Gopinathan KP. Metabolism of ethionamide, a second-line antitubercular drug. J Indian Inst Science 1976; 58(1): 16-27.
35. Carlsen L, Harrit N, Holm A. Oxathiiranes as intermediates in the photolysis of sulphines. JCS Perkin I; 1976; 1404-1407.
36. Katori E, Nagano T, Kunieda T, Hirobe M. Facile desulfurization of thiocarbonyl groups to carbonyls by superoxide. A model of metabolic reaction. Chem Pharm Bull 1981; 29: 3075-3077.
37. Dalvi RR, Poore RE, Neal RA. Studies on the metabolism of carbon disulfide by rat liver microsomes. Life Sci 1974; 14: 1785-1796.
38. Kamataki T, Lin MC, Bekher DH, Neal RA. Studies of the metabolism of parathios with an apparently homogeneous preparation of rabbit liver cytochrome P-450. Drug Metab Dispos 1976; 4: 180-189.
39. Ruse MJ, Waring RH. The effect of methimazole on thioamide bioactivation and toxicity. Toxicol Lett 1991 (in press).