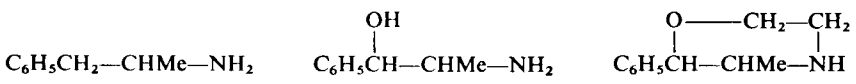
The Metabolism of Phenmetrazine in Man and Laboratory Animals

RONALD B. FRANKLIN, L. GRAHAM DRING
and R. TECWYN WILLIAMS

Department of Biochemistry, St. Mary's Hospital Medical School, London W2 1PG, U.K.

Phenmetrazine (3-methyl-2-phenylmorpholine, compound III; Preludin) is a member of a group of anorexic drugs based on amphetamine or 2-amino-1-phenylpropane (compound I). The metabolism of two of these drugs, amphetamine and methamphetamine, and of the related norephedrine (compound II) has already been studied in this laboratory (Dring *et al.*, 1970; Caldwell *et al.*, 1972; Sinsheimer *et al.*, 1973).

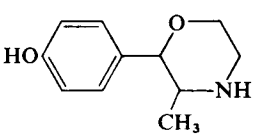


I II III

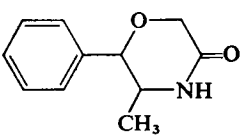
[^{14}C]Phenmetrazine [(±)-*trans*-3-methyl-2-phenyl[2-^{14}C]morpholine] has been synthesized and its fate in man, tamarin monkey, rat and guinea pig examined. As in the case of the other amphetamines mentioned above marked species variations have been found.

When given orally to rats, 68% of the dose (20mg/kg) of ^{14}C was excreted in the urine in 24h, approx. 11% being present as unchanged phenmetrazine. Three compounds (metabolites 1, 2 and 3) were detected in the urine by radiochromatogram scanning. The major compound (metabolite 1) was isolated from urine at pH 8 by continuous extraction with ether and then purified by paper chromatography and t.l.c. Its mass spectrum showed a parent ion at *m/e* 193 which was shifted to *m/e* 207 after treatment with diazomethane. This suggested that metabolite 1 was a hydroxyphenmetrazine (mol.wt. 193). Further tests showed it to be phenolic. It gave a strong purple colour with diazotized 4-nitroaniline, and its u.v. spectrum in ethanol showed a strong absorption peak at $\lambda_{max.}$ 277nm with a bathochromic shift to 294nm on addition of 0.1M-NaOH. Proton resonance spectroscopy for aromatic protons showed a pseudo AB coupling system/doublet (J_{ortho} = 8Hz) characteristic of a *para*-substituted benzene ring. This evidence suggests that metabolite 1 is probably 3-methyl-2-(4′-hydroxyphenyl)morpholine. It accounted for 37% of the dose of phenmetrazine or 54% of the ^{14}C excreted in 24h and was present in the urine both free and conjugated with glucuronic acid. Metabolites 2 (see below) and 3 occurred in the urine to the extent of 4 and 5% of the dose, respectively.

In the guinea pig 82% of an oral dose (20mg/kg) of the drug was excreted in the urine in 24h, only 6% of the dose remaining unchanged. The major product (50% of the dose) in the urine was metabolite 2 from rat urine together with metabolite 3 (10%). The phenolic metabolite 1 from rat urine was not detected. Metabolite 2 was extracted from guinea pig urine and purified in the same manner as metabolite 1. When the ether extract was subjected to g.l.c.–mass spectrometry, the compound present gave a parent ion at *m/e* 191 and a fragmentation pattern identical with that of an authentic sample of 5-methyl-6-phenylmorpholin-3-one (Clarke, 1962).



Metabolite 1
(phenol)



Metabolite 2
(lactam)

Table 1. *Metabolites of phenmetrazine in different species*

Species	Dose (mg/kg)	^{14}C excreted in 24h (% dose)	% of ^{14}C excreted in 24h as: Unchanged drug	Phenol metabolite 1	Lactam metabolite 2	Metabolite 3
Rat	20	68	16	54	6	7
Guinea pig	20	82	7	0	61	12
Tamarin	0.28	72	46	19	17	15
Man	0.36	70	27	31	29	7

[^{14}C]Phenmetrazine hydrochloride (0.28 mg/kg) was injected intramuscularly into tamarin monkeys. In 24h approx. 72% of the ^{14}C was excreted in the urine and nearly half (33% of dose) of this was in the form of the unchanged drug. By radiochromatogram scanning free and conjugated metabolite 1 (14% of dose), metabolite 2 (12%) and metabolite 3 (11%) were found.

Three adult male subjects took 25mg of [^{14}C]phenmetrazine hydrochloride orally (about 0.36mg/kg). The average excretion of ^{14}C was 70% in 24h. The metabolites found were unchanged drug (19% of dose), metabolite 1 (free and conjugated, 22%) metabolite 2 (19%) and metabolite 3 (5%).

Metabolite 3, a minor metabolite in all four species (see Table 1), has not been obtained in sufficient quantity to be identified, but possibilities are the morpholine-ring-opened form of the lactam metabolite 2 or a phenol derived from 2.

The quantitative results of these experiments are summarized in Table 1 so that the species can be compared. Previous work on the amphetamines (Dring *et al.*, 1970; Caldwell *et al.*, 1972; Sinsheimer *et al.*, 1973) has shown that they undergo relatively extensive aromatic hydroxylation in the rat but not in the guinea pig and as Table 1 shows this is also true for phenmetrazine. Amphetamine and methamphetamine are metabolized in the guinea pig mainly by transformation of the isopropylamine side chain. In phenmetrazine this side chain is incorporated in a morpholine ring, but it is this ring, nevertheless, which is attacked in the guinea pig rather than the aromatic ring.

The results for man and the tamarin monkey are not strictly comparable with the rat and guinea pig since the dose of drug given to the former two species was about 10 times smaller than that given to the latter two species. Further, the tamarin received the drug by intramuscular injection. However, the results suggest that the metabolism of phenmetrazine in man and the tamarin is quantitatively different from that in the rat and guinea pig in that the phenol and lactam are produced in roughly equal amounts and more of the drug is excreted unchanged, in fact nearly 50% in the tamarin.

It is interesting to note that the lactam metabolite 2 has muscle relaxant and tranquillizing properties (Gannon & Poos, 1967) and is a drug in its own right under the name Fenmetramide. It could be in part responsible for the marked tolerance which soon develops to phenmetrazine (Van Praag, 1968). Whether the phenolic metabolite 1 has any biological activity is at present unknown. The metabolic formation of a lactam from a morpholine-containing drug has been reported in man by Giraldi *et al.* (1971) for the trichomonacidal agent, 1-morpholinoethyl-5-nitroimidazole (Nitrimidazine).

R. B. F. is grateful to the Science Research Council for an 'Assist' Award.

Caldwell, J., Dring, L. G. & Williams, R. T. (1972) *Biochem. J.* **129**, 11–22
Clarke, F. H. (1962) *J. Org. Chem.* **27**, 3251–3253
Dring, L. G., Smith, R. L. & Williams, R. T. (1970) *Biochem. J.* **116**, 425–435
Sinsheimer, J. E., Dring, L. G. & Williams, R. T. (1973) *Biochem. J.* **136**, 763–771
Giraldi, P. N., Toxolini, G. P., Dradi, E., Nannini, G., Longo, R., Meinardi, G., Monti, G. & de Carneri, I. (1971) *Biochem. Pharmacol.* **20**, 339–344
Gannon, W. F. & Poos, G. I. (1967) *U.S. Patent* 3,308,121
Van Praag, H. M. (1968) *Drug-induced Dis.* **3**, 281–294