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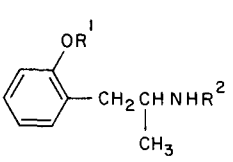
Letter to the Editor

Human metabolism of methoxyphenamine

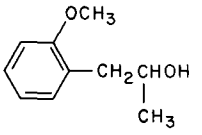
Sir,

Our initial studies of the *in vivo* metabolism of methoxyphenamine (Orthoxine®) in primates were complete[1] before we became aware of a preliminary study of Chundela and Slechtova[2] describing the excretion of methoxyphenamine and two of its metabolites in the urine of man. These workers examined concentrated ether extracts of urine, the pH of which ranged between 5.5 and 6.9, by means of thin-layer chromatography (TLC), gas–liquid chromatography (GLC) and combined gas–liquid chromatography–mass spectrometry (GLC–MS), and showed that three products were present; the major one was unchanged methoxyphenamine (Ia).

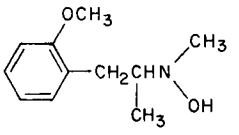


	R^1	R^2
a)	CH_3	CH_3
b)	CH_3	H
c)	H	CH_3

I



II



III

Metabolite 1 was identified correctly by interpretation of its mass spectrum as 2-amino-1-(*o*-methoxyphenyl)propane (Ib) although Chundela and Slechtova[2] named it wrongly as a dimethyl derivative of methoxyphenamine (I) rather than as the N-demethylated derivative of I. They did not compare the TLC, GLC and GLC–MS behaviour of metabolite 1 with an authentic synthetic sample of Ib. In our study[1], such a comparison was made of trifluoroacetylated metabolite 1 and synthetic Ib. The compounds were identical.

Chundela and Slechtova[2] did not identify their metabolite 2 but suggested that it could be either N-hydroxylated methoxyphenamine (III) or a metabolite of the latter, namely 1-(*o*-methoxyphenyl)-2-propanol (II), though they do not interpret their mass spectrum of this metabolite in terms of II or III. We have synthesized II and III to assist us in identifying *in vitro* metabolites of methoxyphenamine[3]. The mass spectra of these compounds (Fig. 1A and B) were clearly different from the reported[2]

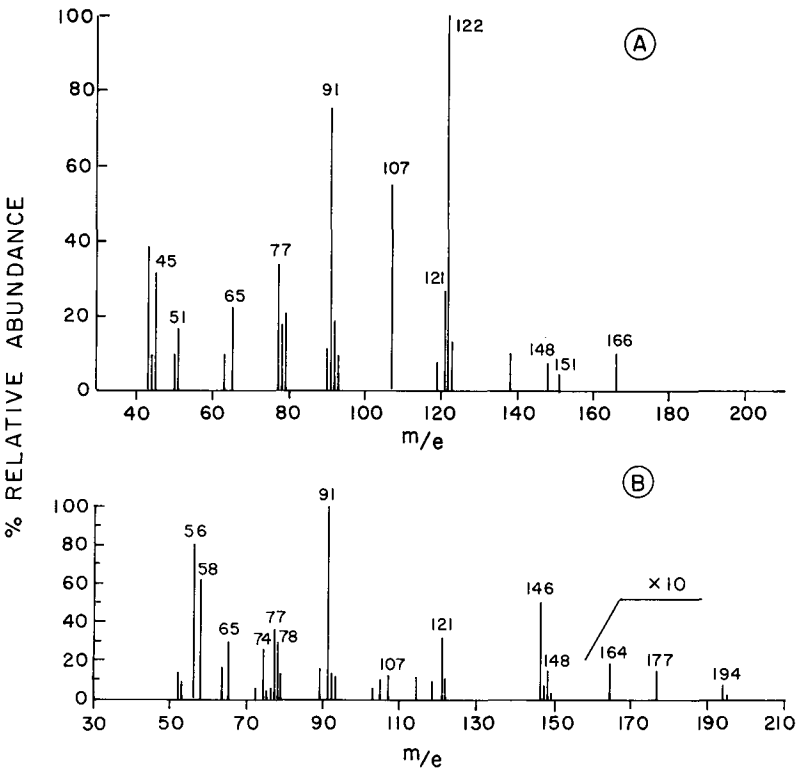


Fig. 1. Normalised mass spectra of II (A) and III (B).

spectrum of metabolite 2. Diagnostic ions observed in the mass spectra of II and III (Fig. 1) are rationalized in Figs. 2 and 3.

A comparison of their spectrum of metabolite 2 with that of our[1] synthetic and metabolically produced 1-(*o*-hydroxyphenyl)-2-(methylamino)propane (Ic) revealed that these spectra were identical, apart from the minor differences expected when different instrumentation is used. Metabolite 2 described by Chundela and Slechtova[2] is therefore the O-demethylated derivative of methoxyphenamine which we found to be the major metabolite of methoxyphenamine in man.

SYNTHESIS OF REFERENCE COMPOUNDS II AND III

Detailed syntheses will be described elsewhere; condensed descriptions are given here.

Preparation of 1-(o-methoxyphenyl)-2-propanol (II)

Reduction of 1-(*o*-methoxyphenyl)-2-propanone with sodium borohydride in methanol gave II as a colorless oil which had infrared, proton magnetic resonance and mass spectra (Fig. 1A) consistent with its structure. GLC analysis on a glass column, 1.8 m × 0.3 cm I.D., packed with 5% OV-225 on Chromosorb W AW DMCS, 100–120 mesh, with nitrogen (60 ml/min) as carrier gas and at oven temperature of 140° gave a single peak, t_r = 2.9 min.

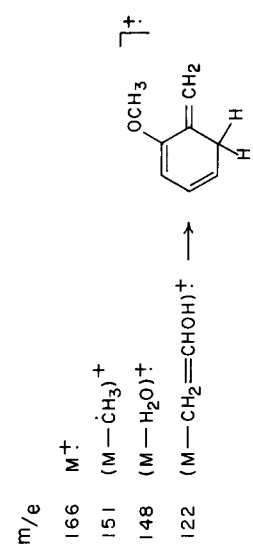


Fig. 2. Postulated mass fragment ions of II.

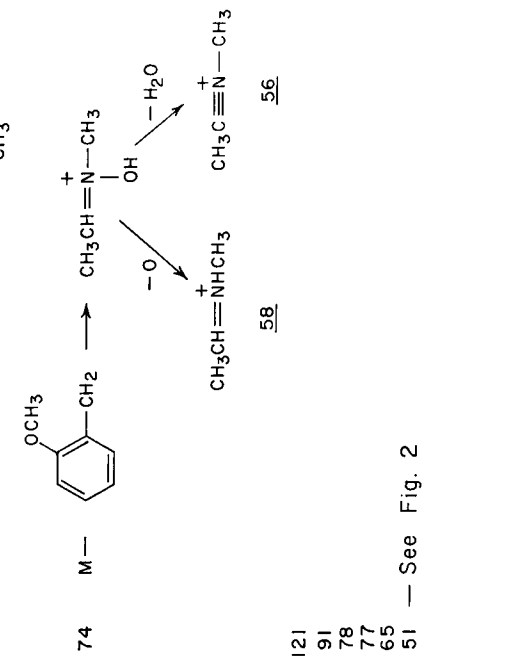


Fig. 3. Postulated mass fragment ions of III.

Preparation of 1-(o-methoxyphenyl)-2-propylhydroxylamine (III)

III was prepared by reductive N-methylhydroxylamination of 1-(*o*-methoxyphenyl)-2-propanone according to the method of Morgan and Beckett[4]. The oxalate salt with m.p. 148–149° analyzed (C,H,N) satisfactorily for the structure. Infrared, proton magnetic resonance and mass spectra (Fig. 1B) were consistent with the structure.

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