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Urinary Excretion and Metabolism of Orally Administered Mefenorex

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Summary

Metabolic pathways and the pharmacokinetic profile of mefenorex ((±)N-(3-chloropropyl)-1-methyl-2-phenylethylamine), and its main metabolite amphetamine (1-methyl-2-phenethylamine) have been studied in two healthy volunteers, after a single oral dose of mefenorex (1.2 mg/Kg b.w. for a male subject and 2.4 mg/Kg b.w. for a female subject). Urinary concentrations were determined by gas chromatography (GC) and metabolite structure was identified by GC/MS following derivatization of urine extracts. The ratio of this metabolite to unchanged drug in urine samples, collected up to 5 h following administration, was essentially the same after either of the administered doses.

The calculated K_{e1} for mefenorex after the higher dose was in the range of 0.191 to 0.272 h^{-1}, with a biological half life ($t_{1/2}$) of 3.98 to 2.55 h, depending on the method of calculation used. The elimination of amphetamine was much slower with a K_{e1} ranging from 0.039 to 0.073 h^{-1} and a $t_{1/2}$ from 9.5 to 17.8 h. Depending on the dose administered, the rate constant of metabolite formation was 0.129 and 0.685 h^{-1} for low and high doses, respectively.

Urinary excretion of Rondimen® amounted to 11.9% within 72 h after administration. Of this amount, 1.5% represented unchanged drug and 10.4% represented metabolites. In addition to amphetamine three other metabolites were identified: p-hydroxy mefenorex, p-hydroxy amphetamine and p-hydroxy-m-methoxy mefenorex.

Key words: mefenorex, pharmacokinetics, metabolism, oral administration

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INTRODUCTION

Therapeutic application of the anorectic and stimulant drug mefenorex is based on its metabolic conversion to its primary metabolite, amphetamine (1-3), and in minor extent on its conversion to p-hydroxy amphetamine (1-3). Therefore, for therapeutically justified drug application it is important that the data on the rate of metabolic conversion of the drug to the main active metabolite are available, as well as the data on the pharmacokinetics of both the drug and the metabolite. In a number of drug testing programs, including testing of athletes, urine sample is used as the most convenient (4). The identification of the metabolite(s) gives, in such a case, additional evidence for the drug having passed through the body. As has been shown in the case of cocaine administration, if the data on the ratios of the drug to metabolite are available for different time intervals after drug administration, estimates on the time of drug administration could also be made (5).

For mefenorex, approximately 1% of a dose is excreted as unchanged drug within 72 hours after oral administration (2,3). Previous studies of mefenorex metabolism in humans (2,3,6,7) have shown formation of p-hydroxy derivatives II and IV (Scheme 1) in addition to amphetamine. In the present study formation of additional metabolite in human is reported, together with the pharmacokinetic parameters estimated from urinary excretion data for both, the drug and the main active metabolite amphetamine.

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MATERIAL AND METHODS

Administration of the drug and sample collection

Mefenorex (Rondimen^{R} dragee; 40 mg/dragee) was given by p.o. route to a male subject at a single dose of 1.2 mg/Kg b.w. and to a female subject at a single dose of 2.4 mg/Kg b.w..

The drug was administered in the morning after the first meal.

Urine samples were collected before drug administration, and in random intervals within 72 hours after drug administration as indicated in Tables I and II. The samples collected were chilled and kept frozen until analyzed.

Chemicals

The following reference compounds were used: Mefenorex hydrochloride (Homburg, Frankfurt/Main, Germany); Dextroamphetamine sulfate (Smith, Kline and French, England).

All other chemicals were analytical grade.

Determination of partition coefficient (log P)

The partition coefficient was determined by partitioning mefenorex between octanol and water phases (8). The concentration in the water layer was determined by UV-spectrophotometry, and that in the octanol was obtained by difference. The partition coefficient was determined as log $P = C_{octanol}/C_{Water}$ (8).

The log P value for mefenorex was also calculated

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according to the method of Rekker (9).

Extraction of urine

1. Extraction of the parent compound and unconjugated metabolites

A 5 mL urine sample, to which 0.5 mL 5N potassium hydroxide and 3 g sodium chloride were added, was extracted with 2 mL of freshly distilled ether. The ether contained phenazine as an internal standard. After extraction, the extract was centrifuged, dried over anhydrous sodium sulfate and subjected to GC analysis.

2. Extraction of conjugated metabolites and derivatization procedures

The urine sample (5 mL) was hydrolysed by heating at 105°C for 30 min after addition of 1 mL of conc.HCl and 10 mg of cysteine. After cooling, the solution was extracted with 5 mL of ether and the extract discarded. The aqueous layer was neutralized with 12M sodium hydroxide and pH adjusted to 9.6 with a solid buffer (2g, sodium bicarbonate/potassium carbonate, 3:2). The sample was extracted into ether/t-butanol (5 mL, 9:1). After drying over anhydrous sodium sulfate, the organic solvent was evaporated under vacuum at 35°C. For GC/MS analysis, evaporated extracts were derivatized to their corresponding trifluoroacetamides and/or trifluoroacatate esters using trifluoroacetic anhydride (TFAA) and ethyl acetate as a solvent. After heating at 65°C for 15 min., the solvent was removed in vacuo and the dry derivatized extract dissolved in anhydrous

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ethyl acetate for GC/MS analysis. Alternatively the extracts were derivatized by the method of selective derivatization (10,11) using N-methyl-N-trimethylsilyl trifluoroacetamide (MSTFA) and N-methyl bistrifluoroacetamide (MBTFA) as derivatizing agents.

Gas chromatography (GC) and gas chromatography/mass spectrometry (GC/MS) of urine extracts

GC analysis was performed on a Shimadzu GC 9A gas chromatograph equipped with fused-silica capillary column (SE-54, 28 m x 0.25 mm ID, SUPELCO): the injector temperature was 180°C and a column temperature was programed at 60°C for 2 min, rising by 20°C/min to 140°C, keeping the final temperature for 5 min. The carrier gas was helium at a flow rate of 0.5 mL/min and the detector was NP FID.

GC/MS analysis was performed on a Kratos MS 25 (Data General Nova 3 Data System) coupled with Perkin Elmer Sigma 3 gas chromatograph. The same column as in GC analysis was used (15 m x 0.20 mm, ID), with an injector port temperature of 285°C (splitless injection) and a column temperature program of 3 min at 100°C, rising by 16°C/min up to 285°C, and keeping the final temperature for 10 min. The carrier gas was helium at a flow rate of 1.2 mL/min. The column was directly coupled to the mass spectrometer. The ion source temperature was 280°C and the ionization mode was electron impact at 70 eV.

Quantization of the compounds in urine samples

The extraction recovery for mefenorex from urine samples

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of known concentration was 98 ± 2%.

Calibration curves were calculated by linear regression for concentrations from 0.1-1.0 µg/mL for mefenorex and 0.1-6.0 µg/mL for amphetamine using phenazine as an internal standard. The calibration curve for mefenorex in the range from 1.0-6.0 µg/mL was determined using non-linear regression. Calibration curves were tested daily using at least three spiked blank urine samples of different concentrations.

Calculation of pharmacokinetic parameters

Pharmacokinetic parameters were calculated from urinary excretion data according to standard procedures described by Wagner (12) and Gibaldi and Perier (13). The results were fitted to the one compartment open model with first order absorption.

The elimination rate constant and the elimination half life for both mefenorex and amphetamine were calculated from: a) the excretion rate, b) the cumulative excretion curves, using the program KINMOD, and c) the elimination curves using the program FARMOK.

The absorption rate constant for mefenorex at the higher dose, and the rate constant for formation of amphetamine were calculated from the simulated blood level curves using computer program FARMOK.

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RESULTS AND DISCUSSION

Figure 1 shows the chromatograms of a methanolic solution (A) and of the extract of a urine sample (B) containing known amounts of mefenorex, amphetamine and the internal standard phenazine. The peak with relative retention time (0.639) arises as a consenquence of thermal degradation of mefenorex. This degradation is proportional with the increase of injector temperature. In order to minimize the degradation, the injector temperature was kept at 180°C. The GC traces showed good resolution of the parent compound from metabolite enabling quantization of both mefenorex and amphetamine in urine samples. The detection limit of this method was 0.1μg/mL for both compounds.

Urinary excretion data for mefenorex and its main active metabolite amphetamine, following oral administration of mefenorex are presented in Tables I-III.

(Tables I-III)
Fig. 1.

Mefenorex and amphetamine were detectable in the urine samples collected up to 11.5 h and 47.5 h, respectively, after oral administration of mefenorex (dose 1.2 mg/Kg b.w.). The concentration of amphetamine in all samples was higher in comparison to mefenorex. Following administration of the higher dose (2.4 mg/Kg b.w.), mefenorex was detectable up to 29 h, and amphetamine up to 72 h after administration (Tables I-III). The ratio of metabolite to

unchanged drug concentrations (A/M) was ~2.5 in the samples collected up to 3.25 h following oral administration of either dose. Also, the A/M ratio in the urine samples collected between 3.25 - 5 h after oral administration of the drug at either dose was similar ~4. However, the A/M ratio in the urine samples collected after the fifth hour following administration of the higher dose (2.4 mg/Kg b.w.) raised to about 30.

Delay in amphetamine excretion and its high urine concentrations, following administration of the higher dose of mefenorex, may be explained by fast tissue distribution of the more lipophilic parent compound, and its fast metabolism to amphetamine following slow release from depot. The lipophilicity of mefenorex, expressed as log P=3.47 (determined experimentally) or log P=3.18 (calculated), was compared with the lipophilicity of amphetamine and methamphetamine (14) as shown in Table IV.

(Table IV)

The overall A/M ratio in the time period of sample collection was 8.8 and 6.9 following administration of lower and higher dose, respectively (Table III).

While the major route of elimination for methamphetamine (15,16) and ethylamphetamine (17), under controlled acidic urinary conditions, is the excretion of the unchanged drug, only 1.5% of orally administered mefenorex was excreted unchanged. Increased metabolism of mefenorex is may be associated with the increased lipophilicity of the nitrogen substituent. As a concenquence the

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excretion of unchanged drug was a minor route of elimination following both doses (Table III). Comparable results have been obtained for metabolism of n-butylamphetamine (18).

Pharmacokinetic parameters

Pharmacokinetic parameters for unchanged drug and amphetamine from urinary excretion data were calculated using different methods for each compound at both doses (Table V);(1) from the cumulative excretion curves (Figs. 2 and 3),(2) from the elimination curves (Fig. 4), and (3) from the plot of the rate elimination rate of the drug (or metabolite) vs. midpoint time (dAu/dt or dMu/dt vs. T). The use of the one compartment-open model for calculations is justified by suggested fast distribution of highly lipophilic mefenorex. Similar assumption regarding distribution and lipophilic properties were made for less lipophilic drugs amphetamine and methamphetamine (19,20).

(Table V)

(Figs. 2, 3 and 4)

The absorption rate constant (K_a) for mefenorex was 2.35 h^{-1} and the constant for formation of the metabolite (K_f) (amphetamine) was 0.685 h^{-1} (Table V) and were calculated from computer simulated blood level curves as shown in Figs. 5A and 5B. The maximal blood concentration for mefenorex was achieved approximately 1.5 h and for amphetamine at approximately 4.5 h

following drug administration. For calculations of blood level curves it was assumed that at the measured pH values of urine between 5.0 and 6.0 (Tables I and II) the amount of the drug excreted in urine reflects the concentration of the drug in blood (Fig.2) (13,21).

Pharmacokinetic parameters for mefenorex after administration of the lower dose could not be calculated from urine excretion data since the values did not achieve plateau in cumulative excretion.

We could not compare pharmacokinetic parameters obtained from urinary excretion data for mefenorex with pharmacokinetic parameters for other racemic N-alkylamphetamines. Extensive studies on urinary excretion of the unchanged drug and metabolite amphetamine have been done after oral administration of the (+) and/or (-) isomers of N-alkylamphetamines (methyl-, ethyl-, n-propyl-, i-propyl, and n-butyl-) (15,17,18,20). However data on racemic N-alkylamphetamines are insufficient for comparison with the present study.

Identification of metabolites

Metabolites were identified by GC/MS monitoring of the total ion current and extracted ion traces. Structures and fragmentation patterns of metabolites identified in urine samples after single oral administration of mefenorex are presented in Scheme 1 and Figs. 6 and 7. In addition to amphetamine (III), three other metabolites were characterized (II, IV and V) (Scheme 1 and

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Figs. 6 and 7).

(Scheme 1)

Metabolites hydroxylated in p-position (II, IV, and V) were identified after derivatization with trifluoroacetic acid anhydride (TFAA) following hydrolysis of the urine sample. Amphetamine (III) and the parent compound (I) were identified in the extracts of urine samples without additional evaporation and derivatization. Compound V, p-hydroxy-m-methoxy mefenorex, was structurally characterized using derivatization with TFAA as well as using the method of "selective derivatization" (10,11). The latter method was used because it produces more stable N-acetyl, O-trimethylsilyl-derivatives. By applying different derivatization reagents to the same sample the proposed fragmentation pattern was confirmed. The mass spectra and fragmentation patterns reported in Figs. 6 and 7 indicate that the metabolic change in the aromatic ring resulted in p-hydroxy-m-methoxy mefenorex. Particularly indicative is the presence of the ions at m/z 425/27 and m/z 410 corresponding to M^+ and $M-CH_3$ of compound V (Fig. 6).

(Figs. 6 and 7)

Based on these identified metabolites, a metabolic pathway for orally administered mefenorex is proposed and presented in Scheme 2.

(Scheme 2)

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REFERENCES:

1. Van Blum J.E. (1969): Experimentelle Untersuchungen mit dem neuen Appetithemmer N-(3-Chloropropyl)-1-methyl-2-phenyl-äthylamin-hydrochlorid (Ro4-5282). Arzneim.-Forsch., 19, 748-755.
2. Caldwell J. (1976): The Metabolism of Amphetamines in Mammals. Drug Metabolism Rev., 5, 216-280.
3. Smith R.L., Dring L.G. (1970): Patterns of Metabolism of β-phenylisopropylamines in man and other species. *in* Amphetamines and Related Compounds., Costa E. and Garattini S. Eds., New York, Raven.
4. Catlin D., Cowan D., Donike M., Fraisse D., Oftebro H., Rendic S. (1992): Testing urine for drugs. J. Aut. Chem., 14, 85-92.
5. Ambre J., RuoT.I., Nelson J., Belknap S. (1988): Urinary Excretion of Cocaine, Benzoylecgonine, and Ecgonine Methyl Ester in Humans. J. Anal. Toxic., 12, 301-306.
6. Rendić S. (1989): Drug metabolism in identification of drugs misused in sport by gas chromatography-mass spectrometry. Acta Pharm. Jugosl., 39, 173-180.
7. Rendić S. (1991): Identification of drug metabolites by gas chromatography-mass spectrometry. *in* Drugs in Competitive Athletics, Shipe J.R. and Savoy J. Eds., Blackwell Scientific Publications, 55-60.
8. Fujita T., Iwasa J., Hansch C. (1964): A New Substituent

Constant, π, Derived from Partition Coefficients, J. Am. Chem. Soc., 86, 5175-5180.

9. Rekker R.F. (1977): The hydrophobic fragmental constant, its derivation and application. New York, Elsevier.
10. Donike M. (1975): N-Trifluoroacetyl-O-Trimethylsilyl-Phenolakylamine Darstellung und Massenspezifischer Gaschromatographischer Nachweis. J. Chrom., 103, 91-112.
11. Donike M., Derenbach J. (1976): Die Selective Derivatisierung unter kontrollierten Bedingungen: Ein Weg zum Spuren-Nachweins von Aminen. Z. Anal. Chem., 279, 128-131.
12. Wagner J.G.(1975): Fundamentals of Clinical Pharmacokinetics. Hamilton, Illinois, Drug Intelligence Publications.
13. Gibaldi M., Perrier D. (1982): Pharmacokinetics. New York, Dekker.
14. Grunewald G.L., Pleiss M.A., Gatchell C.L., Pazhenchevsky R., Rafferty M.F. (1984): Gas Chromatographic Quantitation of Underivatized amines in the Determination of their octanol 0.1M Sodium Hydroxide Partition Coefficient by the Shake-Flask Method. J. Chrom., 292, 319-331.
15. Becket A.H., Rowland M. (1965): Urinary excretion kinetics of methylamphetamine in man. J. Pharm. Pharmac. 17, 109S-114S.
16. Caldwell J., DringL.G., Williams R.T. (1972): Metabolism of [C^{14}]Methamphetamine in Man, the Guinea Pig and the Rat. Biochem. J., 129, 11-22.

17. Becket A.H., Brookes L.G., Shenoy E.V.B. (1969): Urinary excretion of the drug and its main metabolite in man, after the administration of (±), (+) and (-) ethylamphetamine. J. Pharm. Pharmac., 21, 151S-156S.

18. Becket A.H., Shenoy E.V.B., (1973): The effect of N-alkyl chain length and stereochemistry on the absorption, metabolism and urinary excretion of N-alkyl amphetamines in man. J. Pharm. Pharmac. 25, 793-799.

19. Becket A.H., Tucker G.T. (1968): Application of the analogue computer to pharmacokinetic and biopharmaceutical studies with amphetamine type compounds. J. Pharm. Pharmac., 20, 174-193.

20. Vree T.B., van Rossum J.M. (1970): Kinetics of Metabolism and Excretion of Amphetamines in Man. in Amphetamines and related compounds, Costa E. and Garattini S. Eds., New York, Raven Press, 165-190.

21. Becket A.H., Salmon J.A., Mitchard M. (1969): The relation between blood levels and urinary excretion of amphetamine under controlled acidic and under fluctuating urinary pH values using [C^{14}]amphetamine. J. Pharm. Pharmac., 21, 251-258.

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TABLE I: Urinary excretion of mefenorex and its metabolite amphetamine after oral administration of Rondimen^{R} (male subject dose 1.2 mg/kg b.w.). Each value is the mean of at least three determinations.

Excretion interval (h)	urine pH	Amount excreted in intervals (µg/ml)		Ratio A/M
		Mefenorex (M)	Amphetamine (A)	
0 - 3.25	6.5	0.24	0.57	2.4
3.25 - 5.0	6.0	0.38	1.4	3.7
5.0 - 7.25	5.5	0.36	1.58	4.4
7.25 - 9.75	5.5	0.25	1.14	4.6
9.75 - 11.5	5.5	0.31	1.54	4.9
11.5 - 13.5	6.0	-	1.1	-
13.5 - 20.75	5.5	-	1.47	-
20.75 - 23.75	6.0	-	0.91	-
23.75 - 27.7	5.5	-	0.76	-
27.7 - 30.0	6.0	-	0.35	-
30.0 - 34.75	5.5	-	1.03	-
34.75 - 37.25	6.0	-	0.31	-
37.25 - 39.0	6.0	-	0.32	-
39.0 - 43.0	5.5	-	0.56	-
43.0 - 47.5	5.0	-	0.95	-
47.5 - 51.0	5.5	-	-	-
51.0 - 72.0	5.5	-	-	-

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TABLE II: Urinary excretion of mefenorex and its metabolite amphetamine after oral administration of Rondimen^{R} (female subject dose 2.4 mg/kg b.w.). Each value is the mean of least three determinations.

Excretion interval (h)	urine pH	Amount excreted in intervals (µg/ml)		Ratio A/M
		Mefenorex (M)	Amphetamine (A)	
0 - 3.25	5.5	4.0	10.19	2.5
3.25 - 5.33	5.5	4.7	19.77	4.2
5.33 - 9.5	5.5	3.1	30.33	9.8
9.5 - 12.42	5.5	0.67	6.6	9.9
12.42 - 24.75	5.5	0.25	6.98	27.9
14.75 - 21.7	5.5	-	3.1	-
21.7 - 23.8	6.0	-	2.0	-
23.8 - 29.0	5.5	0.11	4.26	38.7
29.0 - 31.4	5.5	-	2.84	-
31.4 - 35.5	5.5	-	0.97	-
35.5 - 40.0	6.0	-	0.67	-
40.0 - 49.2	5.5	-	1.19	-
49.2 - 54.0	6.0	-	0.37	-
54.0 - 57.0	7.5	-	-	-
57.0 - 60.0	7.5	-	-	-
60.0 - 64.6	5.5	-	0.59	-
64.6 - 71.0	5.5	-	0.45	-

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TABLE III: Cumulative amounts of urinary excreted mefenorex and its main metabolite amphetamine over period of 72 hours following oral administration of Rondimen[R]

Dose (mg)	Excretion of mefenorex (M)		Excretion of amphetamine (A)		Ratio A/M
	mg	%	mg	%	
40[a]	0.25	0.63	2.2	5.5	8.8
80[b]	1.21	1.5	8.4	10.4	6.9

[a] Mefenorex was detectable up to 11 h and amphetamine up to 47.5 h after administration of Rondimen[R] (1.2 mg/kg b.w.).
[b] Mefenorex was detectable up to 29 h and amphetamine up to 54 h after administration of Rondimen[R] (2.4 mg/kg b.w.).

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TABLE IV: log P values determined experimentally and calculated by the method of Rekker (9).

Compound	log P	
	Calculated	Experimental
Mefenorex	3.18	3.47
Metamphetamine	2.28*	2.16*
Amphetamine	1.98*	1.81*

* From ref. 14

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TABLE V: Pharmacokinetic parameters for mefenorex and metabolically derived amphetamine following single oral doses of mefenorex, calculated from urinary excretion data

	AMPHETAMINE		MEFENOREX	
	Dose		Dose	
	1.2	2.4	1.2	2.4
	mg/kg b.w.		mg/kg b.w.	
$K_{el}(h^{-1})$	0.039[1]	0.062	-	0.191
	0.053[2]	0.052	-	0.174
	0.040[3]	0.073	-	0.272
$t_{1/2}(h)$	17.8[1]	11.2	-	3.63
	13.1[2]	13.3	-	3.98
	17.3[3]	9.5	-	2.55
$K_a(h^{-1})$	-	-	-	2.35[4]
$K_f(h^{-1})$	0.129[4]	0.685	-	-
$A_u(mg)$	2.41	8.51	-	1.19

Legend:
K_{el} = elimination rate constant
K_a = absorption rate constant
K_f = rate constant for formation of the metabolite (amphetamine)
A_u = cumulative amount of uncharged drug excreted up to 72 h
$t_{1/2}$ = elimination half-life
1 = calculated from the elimination curves
2 = calculated from the elimination rate
3 = calculated from the cumulative excretion curves
4 = calculated from the simulated plasma concentration - time curves

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FIGURE CAPTIONS

Fig.1 A: GC traces of the methanolic solution containing mefenorex (6 µg/mL), amphetamine (25 µg/mL) and phenazine (10 µg/mL).

B: GC traces of the extract of urine samples spiked with the same amount of the compounds as in A.
Relative retention time (RRT): 1. amphetamine 0.283
2. mefenorex 0.856
3. phenazine 1.000

Fig.2 Cumulative elimination of amphetamine in urine after oral administration of mefenorex (dose 1.2 mg/Kg b.w.).

Fig.3 Cumulative elimination of mefenorex (A) and amphetamine (B) in urine after oral administration of mefenorex (dose 2.4 mg/Kg b.w.).

Fig.4 Elimination curves of mefenorex (A) and amphetamine (B) constructed from the urinary excration data, after oral administration of mefenorex (dose 2.4 mg/Kg b.w.), using computer program FARMOC.

Fig.5 Plasma concentration-time curves for mefenorex (A) and amphetamine (B) calculated by the computer program FARMOC from urinary excration data, afte oral administration of mefenorex (dose 2.4 mg/Kg b.w.).

Fig.6 Mass spectrum and fragmentation patterns of p-hydroxy-m-methoxy mefenorex extracted from urine after oral administration of mefenorex (derivatized by "selective derivatization" procedure).

Fig.7 Mass spectrum and fragmentation patterns of p-hydroxy-m-methoxy mefenorex extracted from urine, after oral administration of mefenorex (derivatized using TFAA).

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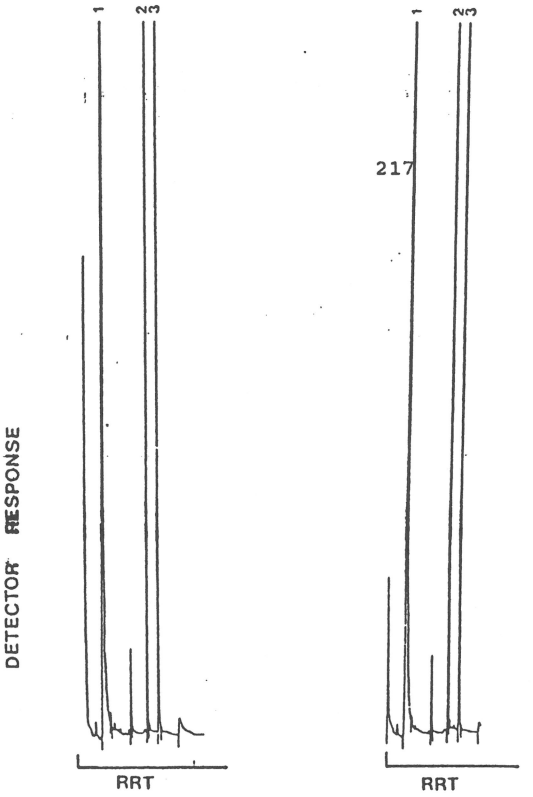

Fig. 1

In: Donike, H. Geyer, A. Gotzmann, U. Mareck-Engelke, S. Rauth (eds.)
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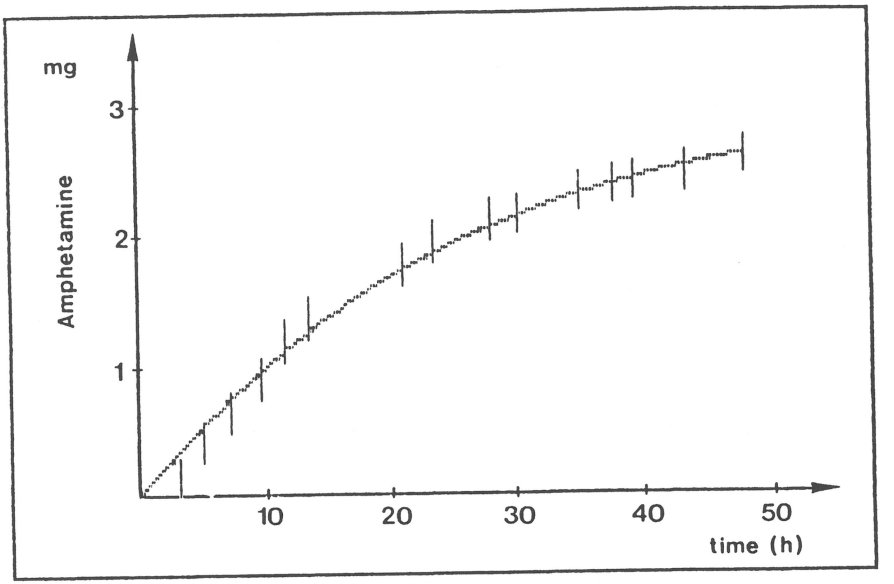

Fig. 2

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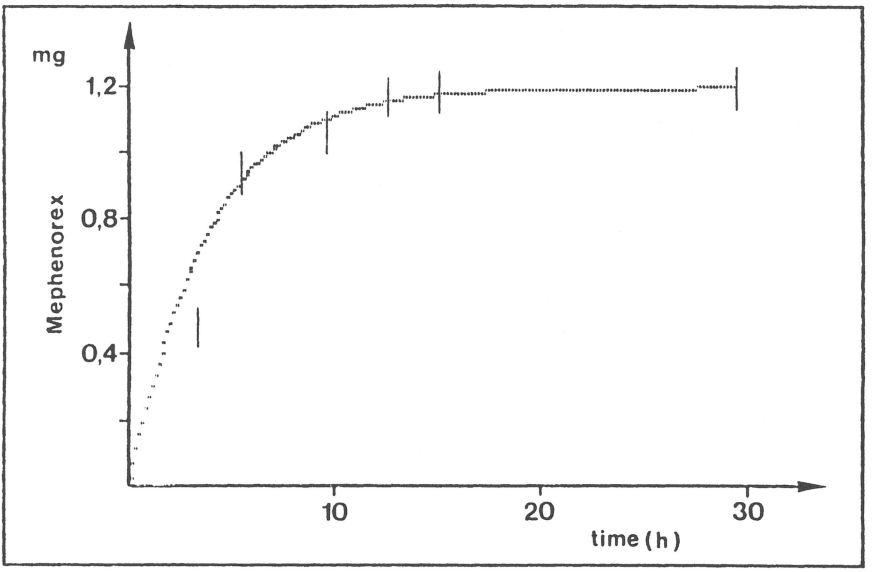

Fig. 3A

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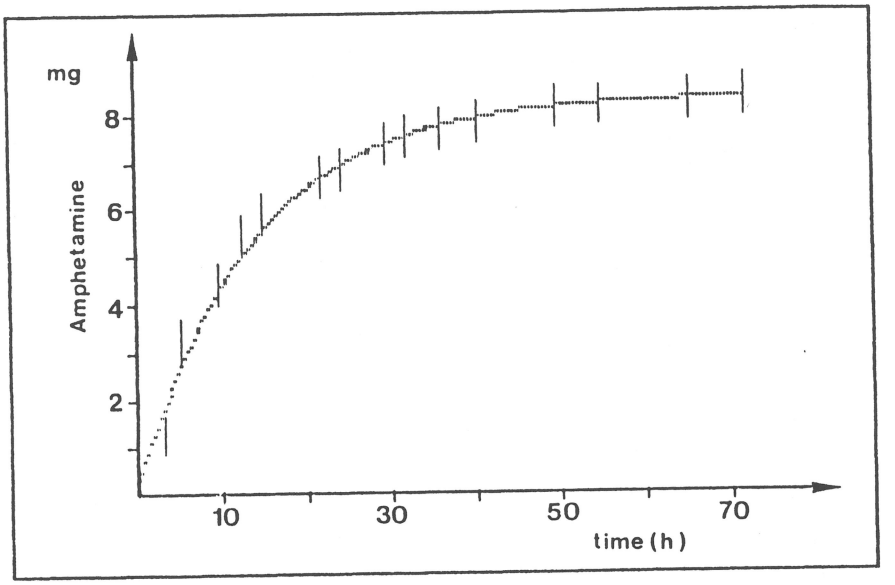

Fig. 3B

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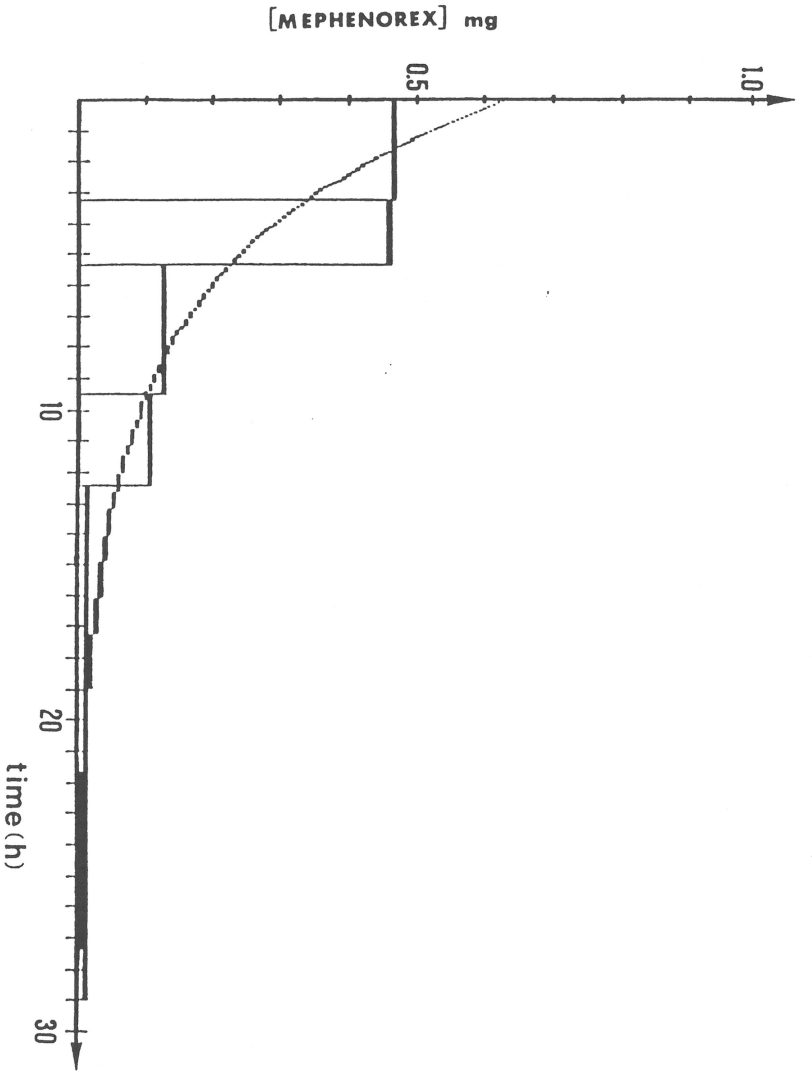

Fig. 4A

In: Donike, H. Geyer, A. Gotzmann, U. Mareck-Engelke, S. Rauth (eds.)
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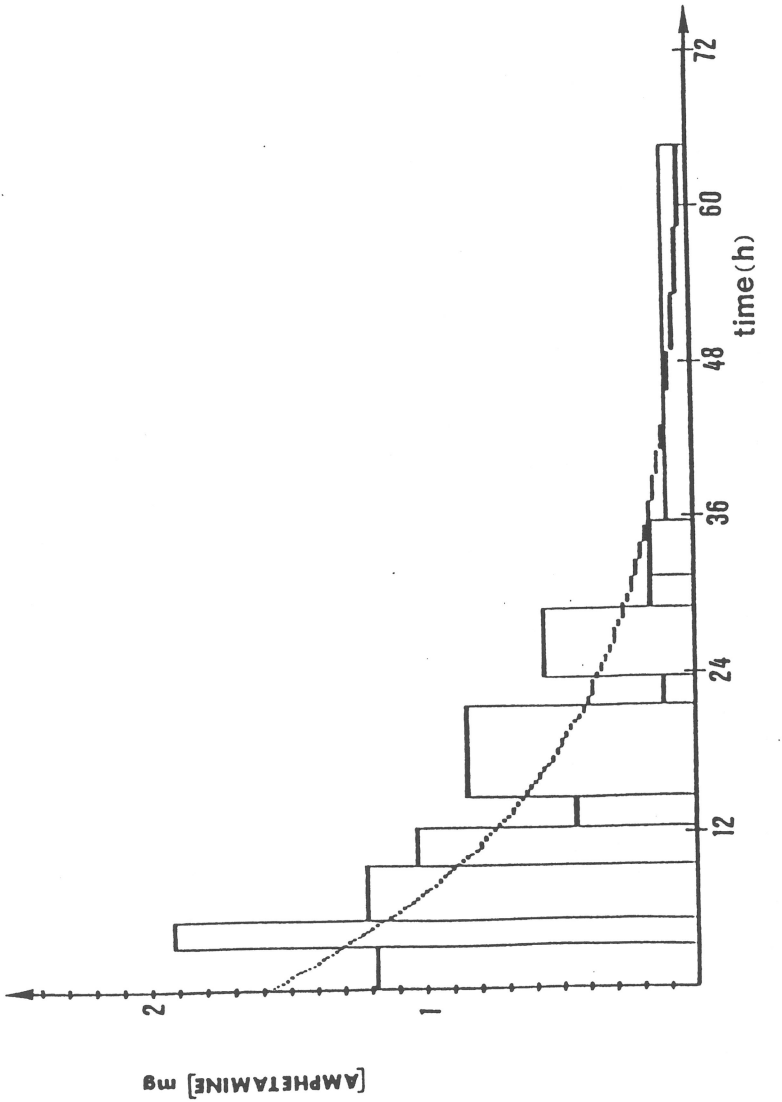

Fig. 4B

In: Donike, H. Geyer, A. Gotzmann, U. Mareck-Engelke, S. Rauth (eds.)
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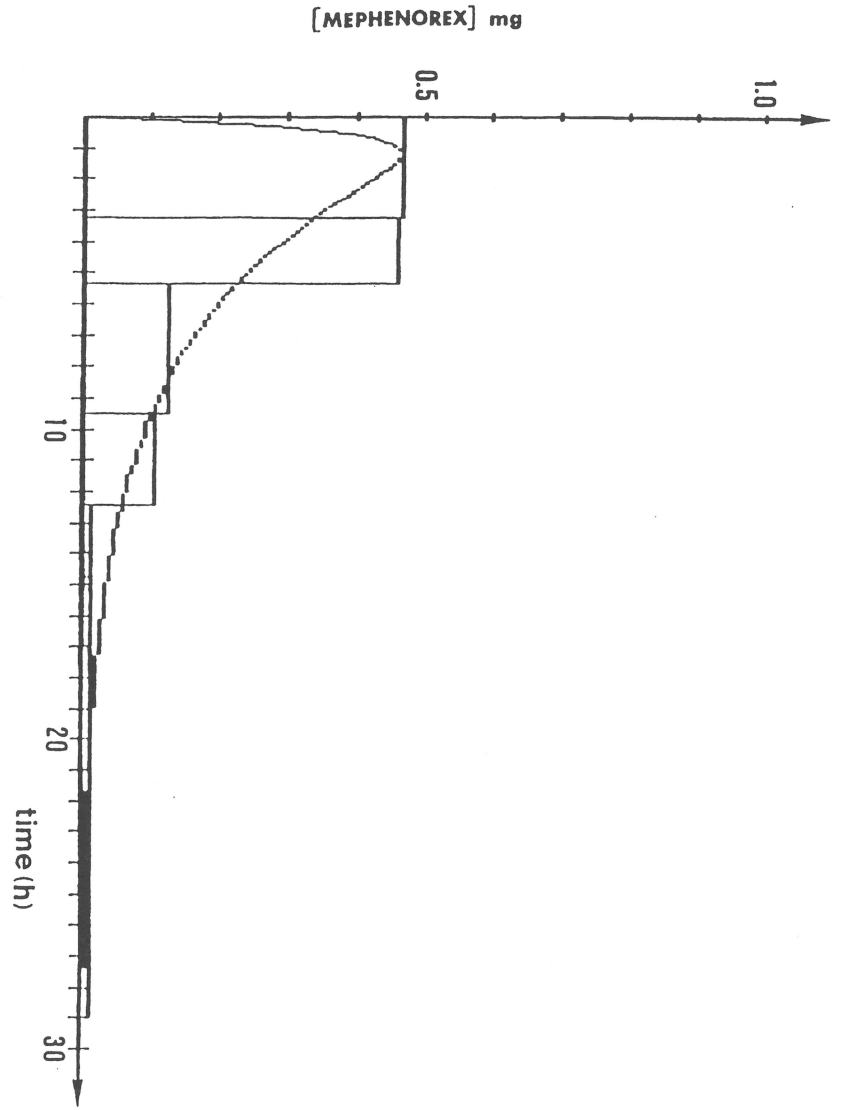

Fig. 5A

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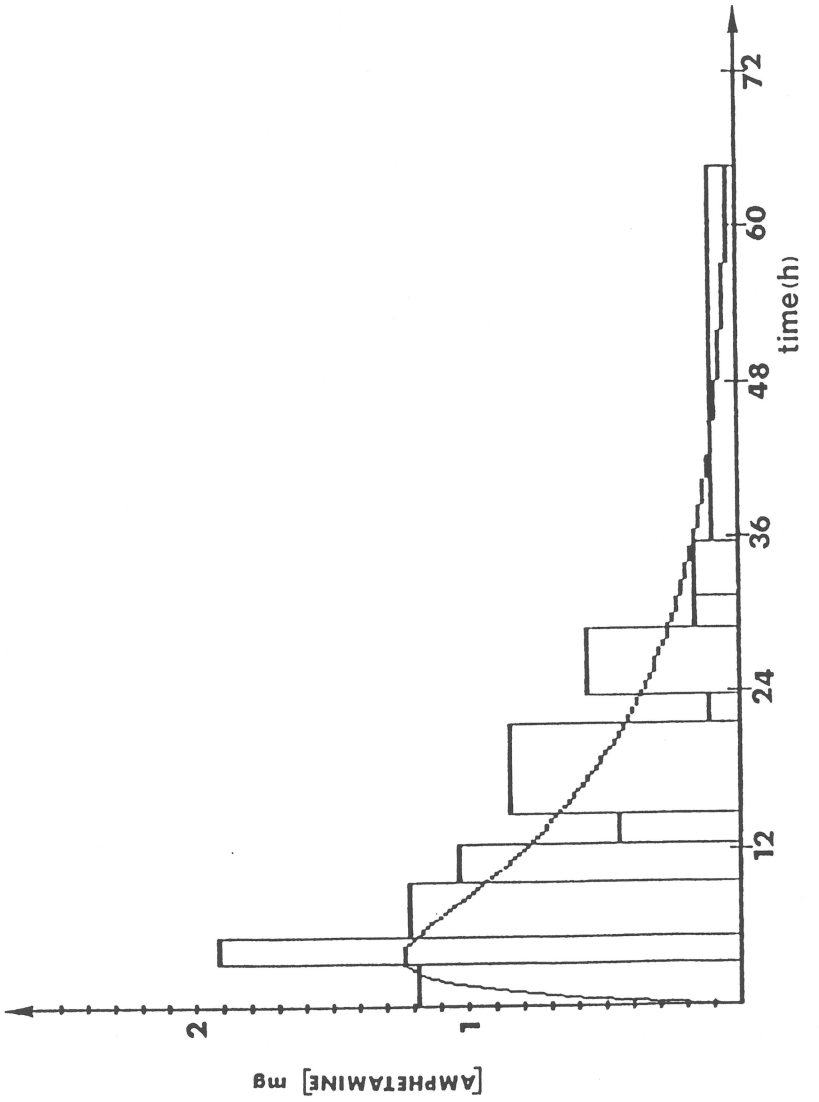

Fig. 5B

In: Donike, H. Geyer, A. Gotzmann, U. Mareck-Engelke, S. Rauth (eds.)
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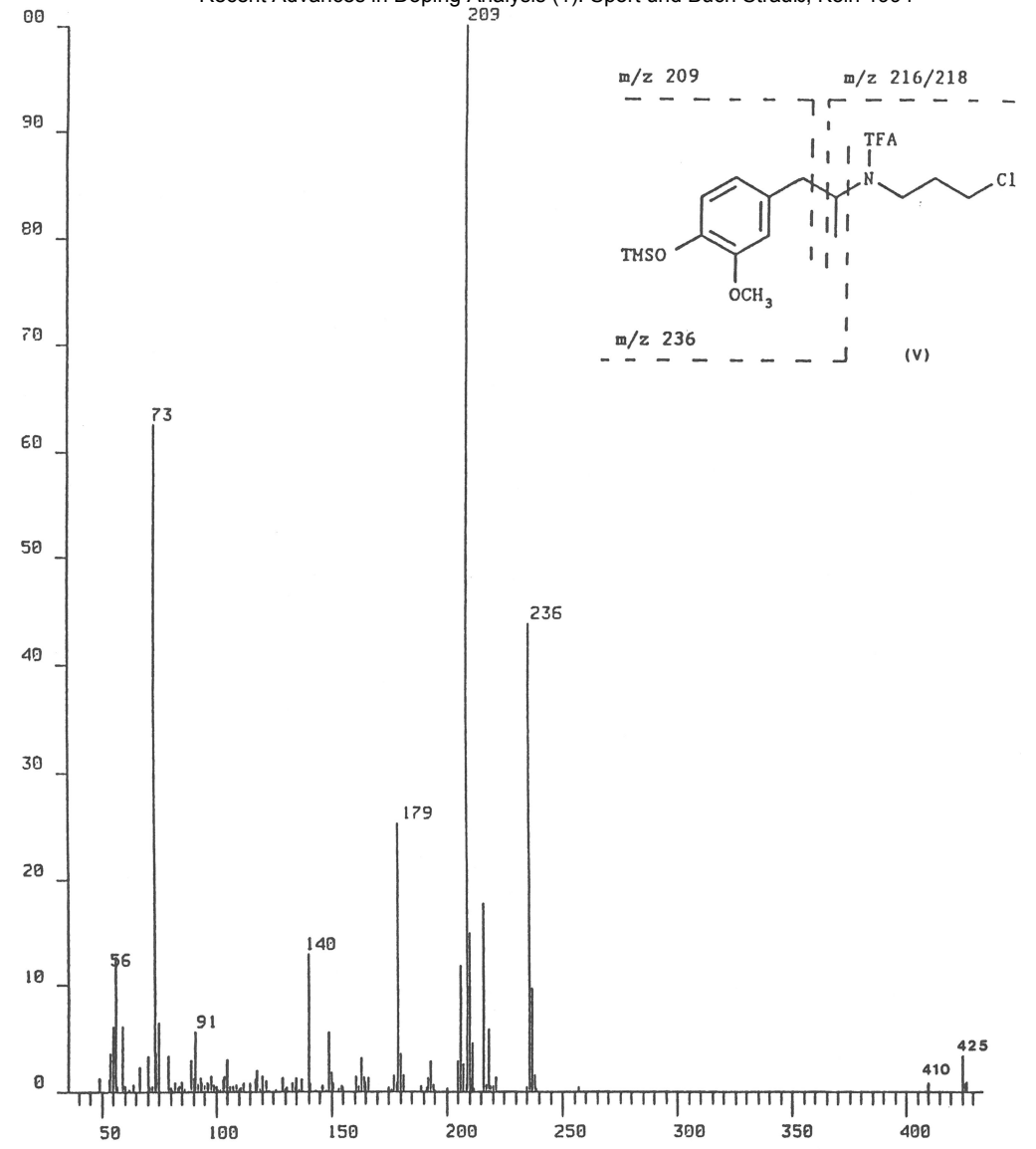

Fig. 6

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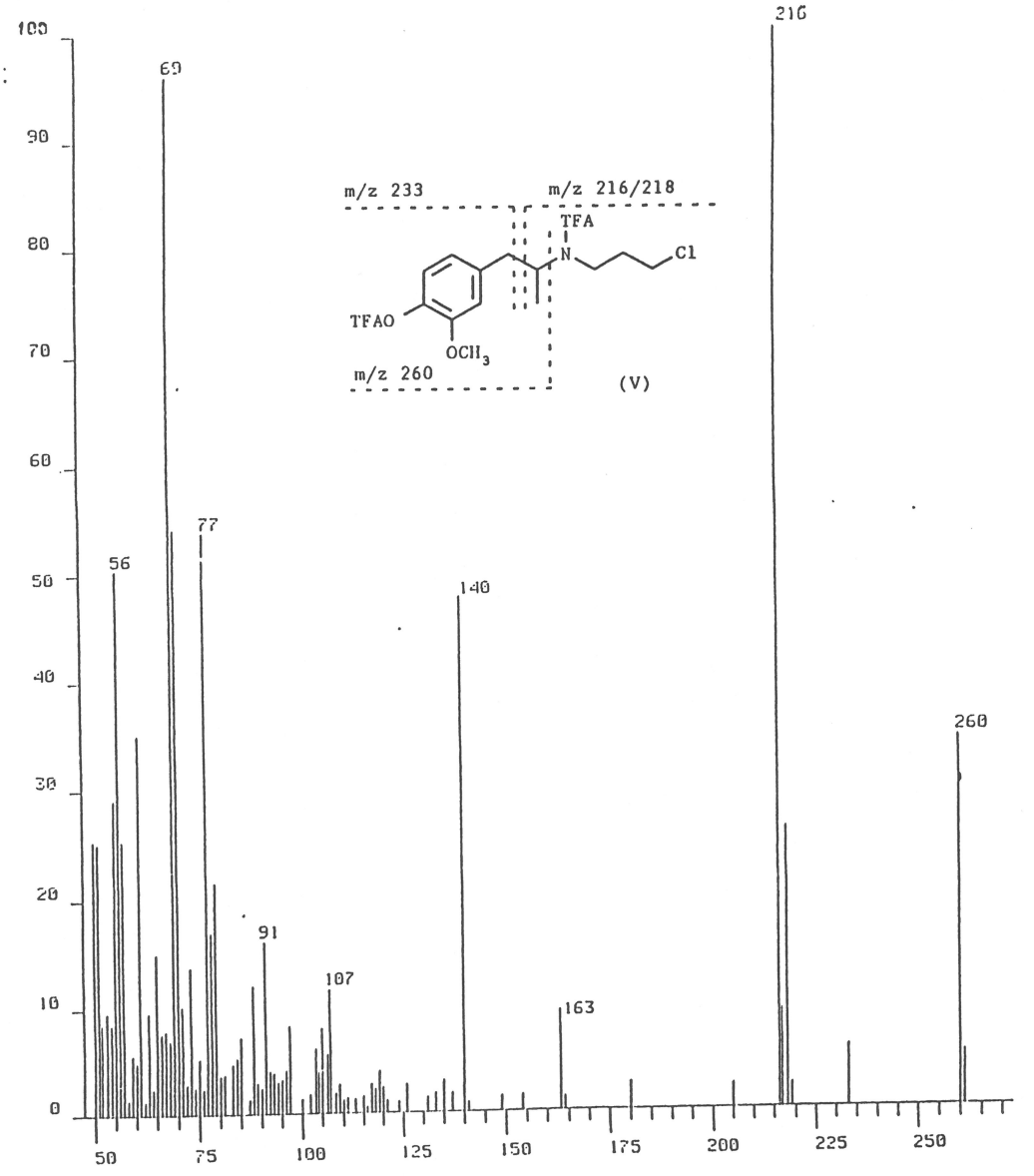

Fig. 7

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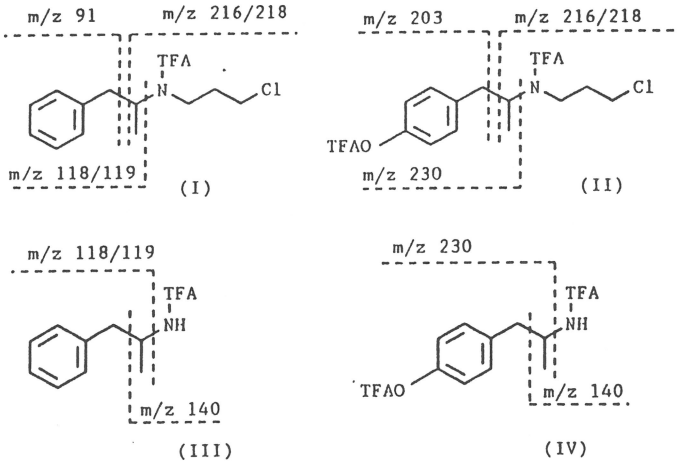
SCHEME 1. Fragmentation pattern of mefenorex (I) and metabolites II-IV.



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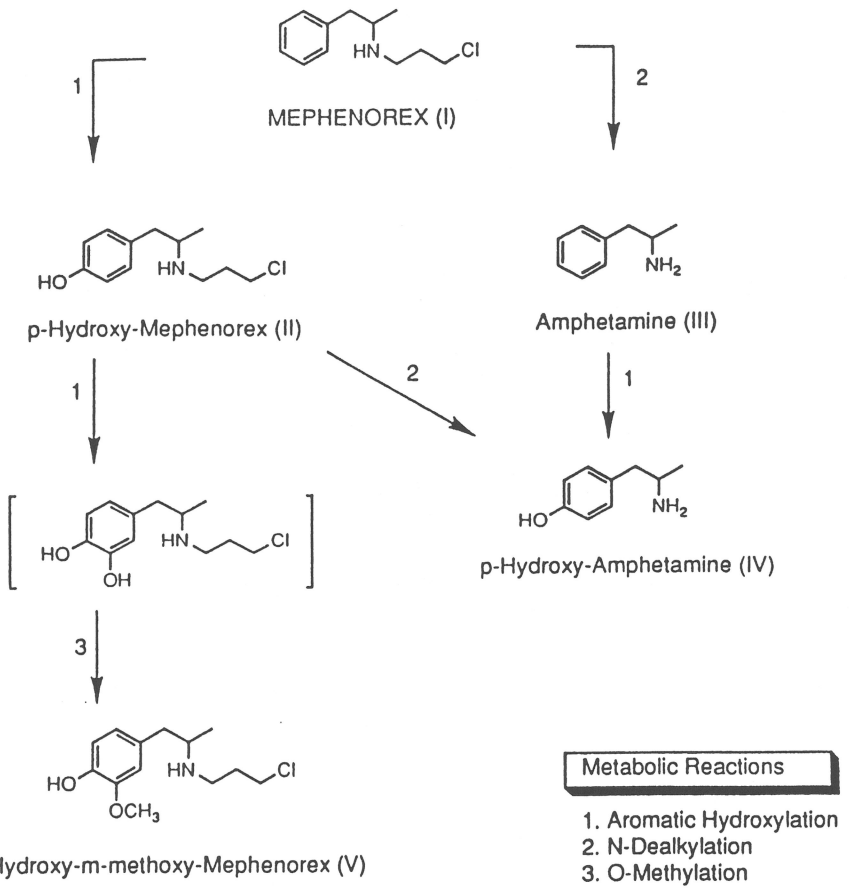
MEPHENOREX- METABOLISM



Scheme 2

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