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#### 1. Introduction

Phenylpropanolamine hydrochloride belongs to the sympathomimetic amine class of drugs and is structurally related to ephedrine hydrochloride. Its synthesis was first reported in 1910 (1) and the first American patent was registered in 1939. The effects of phenylpropanolamine hydrochloride are largely the result of alpha-adrenergic agonist activity resulting from both direct stimulation of adrenergic receptors and release of neuronal norepinephrine. The principal adverse effect of phenylpropanolamine hydrochloride is dose-related hypertension and ventricular arrhythmia has been described (2). Phenylpropanolamine hydrochloride is widely used as a decongestant and it has been used as an anorectic agent for over 40 years (3). A report in 1939 (4) described its effect as an hypertensive agent when administered parenterally.

2. Description

# 2.1 Name, Formula, Molecular Mass

Phenylpropanolamine hydrochloride, sometimes referred to as dl-norephedrine can also be named in a number of ways :

(a)  $\alpha$ -(1-aminoethyl)benzenemethanol hydrochloride

(b) q-(1-aminoethyl)benzyl alcohol hydrochloride

(c) (<sup>+</sup>)-2-amino-phenylpropan-1-ol hydrochloride

(d) 2-amino-1-phenyl-1-propanol hydrochloride

(e) α-hydroxy-β-aminopropylbenzene hydrochloride

(f) 1-phenyl-2-amino-1-propanol hydrochloride



C9H13NO

MM 187.67

#### 2.2 Trade Names

Propadrine, Control, Obestat and Dietac. Numerous products containing phenylpropanolamine hydrochloride in combination with other active ingredients are commercially

available as appetite suppresants and cold and influenza remedies.

# 2.3 Appearance, Odour and Colour

The compound is a white crystalline powder with an odour resembling that of crude benzoic acid.

#### 3. Synthesis

Phenylpropanolamine hydrochloride is prepared by reacting benzaldehyde with nitroethane in 95% ethanol in the presence of sodium hydroxide to form  $\alpha$ -(1-nitroethyl)benzyl alcohol and then reducing this nitro-alcohol to the corresponding amino compound. A stream of hydrogen chloride passed into a suitable solution of the base yields the hydrochloride (5).

# 4. Physical Properties

# 4.1 Solubility

The sample is sonicated for one minute at ambient temperature.

Solvent	mg/ml	Solubility
Water	≥50-<1000	Soluble
Methanol	≥50-<1000	Soluble
Isopropanol	≥10-<33.3	Sparingly soluble
Diethylether	<0.5	Practically insoluble
Ethyl acetate	<0.5	Practically insoluble
Chloroform	<0.5	Practically insoluble
Benzene	<0.5	Practically insoluble
Carbon tetrachloride	<0.5	Practically insoluble
Acetonitrile	<0.5	Practically insoluble
Acetone	<0.5	Practically insoluble
Cyclohexane	<0.5	Practically insoluble

# 4.2 Melting range

Phenylpropanolamine hydrochloride crystals melt at 190-194°C. The free base melts at 101-101.5°C (6).

# 4.3 Specific Rotation

The specific rotation,  $\left[\alpha\right]_{D}^{25}$ , of phenylpropanolamine hydrochloride in water is +32° (7).

# 4.4 Crystal Structure

The crystal structure was determined using single crystals of phenylpropanolamine hydrochloride obtained by slow evaporation of an aqueous solution at room temperature. The intensity data were collected on an automatic four-circle diffractometer using Ni-filtered  $CuK_{\alpha}$  radiation. Phenylpropanolamine hydrochloride has a monoclinic crystal system with possible space groups of  $P_{2_1}$  (non-centrosymmetric) or  $P_{2_1}/m$  (centrosymmetric). The cell dimensions are a = 7.448Å, b = 9.461Å, c = 14.595Å,  $\beta$  = 103.4° with each asymmetric unit containing two molecules (8).

#### 4.5 Dissociation Constant

The pK of phenylpropanolamine hydrochloride determined potentiometrically at 20°C is  $9.44 \stackrel{+}{-} 0.04$  (9).

# 4.6 Infrared Spectrum

The infrared spectrum of phenylpropanolamine hydrochloride is shown in Figure 1. It was obtained from a Nujol mull between KBr plates using a Perkin-Elmer 180 Infrared Spectrophotometer. Characteristic band assignments are listed below.

Frequency (cm <sup>-1</sup> )	Assignment
3368	O-H stretching
3303	NH2 <sup>+</sup> stretching
2800-2400	NH3 <sup>+</sup>
1990	NH2 <sup>+</sup>
1623	$NH_3^{3+}$ out of plane deformation
1598	C=C aromatic stretching
1581	NH3 + out of plane deformation
1508, 1491	C=C aromatic stretching
1450	O-H out of plane deformation
1329	NH <sub>2</sub> <sup>+</sup> in plane deformation
1241, 1208	O-H in plane deformation
1128, 1088, 1054	C-H in plane deformation,
	monosubstituted benzene
1031	C-O stretching
816, 802	NH <sub>2</sub> <sup>+</sup> rocking
747, 703	C-H out of plane deformation,
	monosubstituted benzene





# 4.7 Differential Scanning Calorimetry

Phenylpropanolamine hydrochloride was heated from 320 to 520°K at a rate of 20°/minute under an atmosphere of nitrogen in a Perkin-Elmer Model DSC-2 Differential Scanning Calorimeter. The thermogram is depicted in Figure 2. A single endotherm was observed with an onset temperature of 194.5°C which corresponds to the melting point. The heat of transition ( $\Delta$ H melting) calculated in relation to an indium standard is 168  $\frac{+}{-}$  6 Jg<sup>-1</sup>.

# 4.8 Proton Magnetic Resonance Spectrum

The 60 MHz proton magnetic resonance spectrum of phenylpropanolamine base was obtained with a Perkin-Elmer Model R-12 Spectrometer. The spectrum in CDCl<sub>3</sub> with tetramethylsilane (TMS) as the internal standard is depicted in Figure 3. The integration and multiplicities are consist-



Figure 2. Differential scanning calorimetry curve of phenylpropanolamine hydrochloride.



CDCl3. Proton magnetic resonance spectrum of phenylpropanolamine in Figure 3.

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ent with the proton assignments. Chemical shifts ( $\delta$ ) in ppm relative to TMS are :

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Proton assignment	Number of protons	J(Hz)	Chemical Shift (δ)	Multiplicity
-CH3	3	9.0	0.94	Doublet
-NH, -OH	3	-	2.07	Singlet
N-C-H	1	9.0	3.12	Quintuplet
O-C-H	1	9.0	4.51	Doublet
Aromatic	5	-	7.41	Singlet

An inspection of the D<sub>0</sub>O exchange spectrum shows disappearance of the resonance at 2.07 ppm. This corresponds to three protons, one hydroxyl proton and two amino protons.

#### 4.9 Ultraviolet Spectrum

The ultraviolet spectra of phenylpropanolamine hydrochloride in methanol and 0.1M HCl at a concentration of 1 mg/ml were obtained with a Beckman Acta M VI ultraviolet spectrophotometer. The spectrum in methanol is depicted in Figure 4. The spectrum obtained in methanol shows shoulders



Figure 4. Ultraviolet spectrum of phenylpropanolamine hydrochloride in methanol.

at 267, 248 and 243 nm whilst in 0.1M HCl shoulders occur at 267, 247 and 242 nm.

Solution	Absorption Maxima (nm)	3
Methanol	264.0	133.63
	258.0	179.04
	252.0	145.44
0.1M HCL	262.8	144.32
	257.0	185.04
	251.0	148.82

# 4.10 Mass Spectrum

The low resolution mass spectrum of phenylpropanolamine hydrochloride is shown in Figure 5. It was obtained with a Varian MAT CH5-DF mass spectrometer. Direct probe at 80°C into the ion source was used to obtain the mass spectrum The molecular ion is not observed. The assignments of some of the major ions formed are :

m/e	010	Ion
132	17	Ph-CH=C(CH <sub>o</sub> )NH <sub>o</sub> <sup>+</sup>
105	29	Ph-C=O <sup>+</sup> 2 2
91	26	Ph-CH_+
77	100	Ph <sup>+ 2</sup>

# 5. Methods of Analysis

#### 5.1 Elemental Analysis

	Theo	Theory (%)	
Element	Hydrochloride	Base	
C	57.62	70.61	
Н	7.47	9.80	
N	18.92	9.15	
0	7.46	10.44	
Cl	8.52	-	

# 5.2 Ultraviolet Spectrophotometric Analysis

Periodate oxidation of phenylpropanolamine hydrochloride has been used. The sample to be determined is placed in a separatory funnel, sodium bicarbonate and sodium metaperiodate are added and after standing for about 15 minutes the solution is extracted with hexane after the addition of 1M hydrochloric acid. The extract is filtered and the



absorbance determined at 242nm in 1cm cuvettes using hexane as the reference. The amount of the oxidation product of phenylpropanolamine hydrochloride is determined by comparison of the sample absorbance against the absorbance of a Phenylpropanolamine Hydrochloride Reference Standard treated in the same manner (10). Ether (11) and chloroform (12) have also been used for the extraction of the derivative. Wallace (13) used alkaline periodate oxidation to form benzaldehyde which was subsequently converted to the semicarbazone derivative, thus enhancing the specificity and sensitivity of the procedure. Phenylpropanolamine hydrochloride has also been determined after alkaline extraction into an organic solvent followed by back-extraction under aqueous acidic conditions (14).

# 5.3 Colorimetric Analysis

Phenylpropanolamine hydrochloride can be reacted with ninhydrin in a citrate buffer at an elevated temperature and determined colorimetrically at 570nm (15). This reaction has been applied to the determination of phenylpropanolamine hydrochloride in a multicomponent mixture by an automated system which, after phase separation, utilizes the stream splitting technique to divide the chloroform stream into segments (16). An ion-pair extraction technique using an acidic dye, bromothymol blue, has been utilized and the resulting chloroform extract determined at 420nm (17).

# 5.4 Spectrofluorimetric Analysis

Phenylpropanolamine hydrochloride has been determined by measuring its fluorescamine derivative, 4-phenylspiro[furan-2(3H),1'-phthalan]-3,3'-dione at 480nm whilst exciting at 398nm (18). The reaction favours a pH of 9 for optimal reactivity (19).

# 5.5 Titrimetric Analysis

After extraction of phenylpropanolamine hydrochloride from an alkaline aqueous solution with chloroform, shaking with saturated sodium chloride solution and backextracting with an excess of sulphuric acid, the excess acid is titrated with a standard sodium hydroxide solution using methyl red as indicator (20).

# 5.6 Chromatographic Analysis

# 5.6.1 Column Chromatography

A weakly basic anion exchange resin, Amberlite IR-45, was found to be suitable for the separation of phenylpropanolamine hydrochloride from various dosage forms and vielded a 99.6% recovery of the drug which was then determined titrimetrically (21). Being a nitrogenous base, the drug is retained on a sulphonated polystyrene cation exchange resin. Determination is then effected by measuring the ultraviolet absorption after elution with hydrochloric acid (22, 23). Phenylpropanolamine hydrochloride has been determined by mixing with ammonium hydroxide, the base eluted with chloroform from a Celite column and the absorbance measured at 258.5nm (24). Separation of phenylpropanolamine hydrochloride from mixtures of drugs in various dosage forms has been described. The method involves the retention of phenylpropanolamine on the first of four Celite columns followed by elution, addition of sodium hydroxide, extraction of the free base with chloroform and subsequent determination at 257nm using sulphuric acid as the reference solution (25). An on-column periodate oxidation of phenylpropanolamine to benzaldehyde on a weakly basic Celite column has also been described and the derivative determined at 267nm (26).

# 5.6.2 Paper Chromatography

A descending paper chromatographic technique using Whatman No. 1 paper has been reported. The solvent system consisted of a 1:1 mixture of butanol (saturated with 1M hydrochloric acid) and methanol. After spraying with Dragendorff's reagent, the resulting orange-red spots were quantitatively determined by densitometry (27).

# 5.6.3 Thin Layer Chromatography

A number of thin layer chromatographic systems have been described for phenylpropanolamine hydrochloride and these are listed in Table 1.

# 5.6.4 Gas Chromatography

Gas chromatography has been extensively used as a method for determining phenylpropanolamine in pharmaceutical preparations and, to a lesser extent, for the determination of the drug in body fluids. The drug has been chromatographed directly without derivatization and also as the silyl, pentafluorophenyloxazolidine, acetone, butanone, trifluoroacetyltrimethylsilyl, heptafluorobutyryl and TABLE 1

# THIN LAYER CHROMATOGRAPHIC SYSTEMS FOR PHENYLPROPANOLAMINE

Solvent System	Adsorbant	Detection	Rf	Reference
Chloroform layer from a mixture of chloroform/ acetic acid/methanol/ water (85:20:8:20)	Silica Gel G (F254) (60µ)	Sprayed with 0.3% p-nitroan- iline plus 5% sodium nitrite, heated at 70°C for 15 minutes then sprayed with 20% sodium carbonate	Not reported	28
Not reported	Silica Gel G (F254) (60µ)	Sprayed with buffer (pH 9.3), oversprayed with fluoresc- amine/acetone solution and re-sprayed with buffer	0.50	19
Benzene/ethyl acetate (70:30) Benzene/ethyl acetate (30:70) Hexane/ethyl acetate (50:50) Hexane/ethyl acetate (30:70)	Gelman ITLC fibre SAF	p-nitrobenzoyl chloride applied and heated (100°C)	0.79 0.90 0.76 0.90	29
Ethyl acetate/methanol/ formic acid (69:30:1)	HPTLC Silica Gel 60	Dipped into o-phthalaldehyde solution followed by 20% polyethylene glycol in methanol	0.40	30

# TABLE 1 (continued)

Solvent System	Adsorbant	Detection	Rf	Reference
Heptane/methanol (60:40) Benzene/methanol (83:17) Benzene/acetone/methanol/ dioxane (40:40:4:5)	HPTLC Silica Gel 60	Fluorescamine solution	0.45 0.37 0.28	31
Ethyl acetate/methanol/ water/ammonia (85:10:3:1)	Silica Gel	Sprayed with 0.3% ninhydrin acid, heated at 100°C for 5 minutes, sprayed with 5% $H_2SO_4$ , heated with hot air for 5 minutes, sprayed with iodoplatinate reagent then p-nitroaniline reagent, heavily sprayed with 25% alcoholic NaOH solution	Not reported	32
Chloroform/methanol (4:1) Chloroform/methanol (4:1)	Silica Gel G Silica Gel G (HF254)	Iodine vapour Iodine vapour	0.17 0.14	33
n-butanol/acetic acid/ water (4:1:5)	DC-cellulose	Ninhydrin reagent	Not reported	34

2,6-dinitro-4-trifluoromethylbenzenesulphonic acid derivatives. The gas chromatographic conditions are listed in Table 2.

# 5.6.5 High Performance Liquid Chromatography

High performance liquid chromatography has been used for the determination of phenylpropanolamine alone and in pharmaceutical formulations but relatively little information has been published on the high performance liquid chromatographic analysis of phenylpropanolamine in biological Table 3 lists the various methods and associated fluids. conditions which have been reported. A technical report issued by Waters Associates describes the following conditions for the determination of phenylpropanolamine : 0.3m x 4mm (i.d.) µBondapak C18 column, methanol/water (50:50) including PIC reagent B-7, detected at 254nm with a retention time of 3.1 minutes for the drug. A similar technical bulletin issued by the Du Pont Company lists the following conditions : 0.25m x 4.6mm (i.d.) Zorbax TMS column, hexanesulphonic acid/ acetic acid/water/methanol (0.1:1:68.9:30), detected at 254nm at a flow rate of 2.5 ml/min and retention time of 2.4 minutes.

# 6. Stability

Phenylpropanolamine hydrochloride is a relatively stable compound. A solid state mixture of phenylpropanolamine hydrochloride, phenylephrine hydrochloride and aspirin in the presence of starch, sugar and talc was stressed at 70°C for 42 days. Phenylpropanolamine hydrochloride was found to be quite stable under these conditions, showing a loss of about 10% when assayed by a thin layer chromatographic method (28). A recent study on phenylpropanolamine hydrochloride in a film-sealed tablet, however, indicated that the molecule is subject to decomposition in pharmaceutical formulations with time at normal and elevated temperatures (52). A significant decrease in phenylpropanolamine hydrochloride concentration was observed in stressed samples when assayed by the periodate oxidation method (11). Stability studies carried out on phenylpropanolamine hydrochloride in a decongestant syrup formulation containing sucrose indicated a reduction in concentration of the drug. Further studies showed decomposition of phenylpropanolamine hydrochloride in the presence of fructose, dextrose and 5-(hydroxymethyl)-2-furaldehyde, but not with sorbitol or levulinic acid. It was speculated that Schiff base formation probably occurred under the test conditions (59).

TABLE 2

GAS CHROMATOGRAPHIC SYSTEMS FOR PHENYLPROPANOLAMINE

Drug Source	Column	Carrier Gas	Column Temp(°C)	R <sub>T</sub> (mins)	Detector	Injected as	Ref
Tablets, syrup	2.0m x 4.0mm (i.d.) glass 0.1% silicone oil (DC- 710) on 60-80 mesh dimethyldichlorosilane treated glass beads	He	200	2.80	FID	Silyl derivative	35
Syrup	2.4m x 3.2mm (o.d.) Pyrex glass 2% SE-30 on Chromo- sorb W (HP)	He	180	1.80	FID	Phenylpropan- olamine	36
Plasma	2.0m x 2.0mm (i.d.) glass 1.25% OV-17 on Gas Chrom Q	<sup>N</sup> 2	190	5.00	FID	Pentafluoro- phenyloxazol- idine deriv- ative	37
Tablets	1.8m x 4mm glass 3% OV-17 on Gas Chrom Q	He	230	0.85	FID	Phenylpropan- olamine	38
Urine	2.0m x 2.2mm stain- less steel 3% OV-1 on Gas Chrom Q	He	230	0.30	Nitrogen	Phenylpropan- olamine	39

		TAE	BLE 2 (cont	tinued)			
Drug Source	Column	Carrier Gas	Column Temp(°C)	R <sub>T</sub> (mins)	Detector	Injected as	Ref
Tablets, capsules, liquids	1.8m x 6.4mm (i.d.) glass 1% HI-EFF-8BP and 10% SE52 on Gas Chrom Q	<sup>N</sup> 2	220	2.40	FID	Phenylpropan- olamine hydrochloride	40
	4% HI-EFF-8BP on Gas Chrom Q		220	1.25			
Raw Material	1.8-2.4m x 3mm (i.d.) glass	Ar	104	9.10	EC	Phenylpropan- olamine	41
	1.15% SE-30 on Gas Chrom P			13.40		Acetone deriv- ative	
				123.50		Butanone deriv- ative	
Raw <sub>.</sub> Material	1.4m x 4mm (i.d.) glass 3% Poly A 103 on Gas Chrom Q	He	Prog- rammed 70-250	28.00	FID	Trifluoroacetyl- trimethylsilyl derivative	42
Serum	1.4m x 3.2mm (o.d.) stainless steel 5% EGS on AW-DMCS Chromosorb W	<sup>N</sup> 2	140	3.70	EC	Heptafluoro- butyryl deriv- ative	43
Raw Material	1.1m x 2.5mm glass 18.8% Apiezon N on Diatoport S	N <sub>2</sub>	180 138 101	2.55 2.77 3.18	FID	Phenylpropan- olamine	44

TABLE 2	(cor	ntin	ued
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Drug Source	Column	Carrier Gas	Column Temp(°C)	R <sub>T</sub> (mins)	Detector	Injected as	Ref
Raw Material	1.8m x 2mm (i.d.) glass 3% OV-1 on Supelcoport	<sup>N</sup> 2	250	1.38	EC	2,6-dinitro- 4-trifluoro- methyl-benzene- sulphonic acid derivative	45
	0.9m x 2mm (i.d.) glass		220	1.38			
	3% SP-2250 on Supel- coport		230	0.98			
Raw Material	1.2m x 4mm (i.d.) glass 2% SE-30 and 2% Carbowax 20M on Anachrom ABS	<sup>N</sup> 2	185	1.60	FID	Phenylpropan- olamine hydro- chloride	46
Raw Material	1.8m x 2mm glass 3% OV-17 on Anachrom ABS	He	Pro- grammed 100-250	8.36	Nitrogen	Phenylpropan- olamine	47
Bio- logical	1.0m x 6mm (o.d.) glass	<sup>N</sup> 2			FID	Phenylpropan- olamine	33
Material	7.5% Carbowax 20M on Chromosorb W		165	4.10			
	2.0% Carbowax 20M on Chromosorb G		120	1.10			
Urine	1.1m x 3mm (i.d.) glass 12.5% Apiezon L on Chromosorb W impregnat- ed with 2% Igepal CO 880	Не	170	Not reported	Nitrogen	Phenylpropan- olamine	34

TABLE 3

HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC SYSTEMS FOR PHENYLPROPANOLAMINE

Drug Source	Column	Mobile Phase	Flow rate (ml/min)	R <sub>T</sub> (mins)	Detection	Ref
Tablets, syrup	0.5m x 2.1mm (i.d.) Du Pont Zipax SCX	0.02M (NH <sub>4</sub> ) <sub>2</sub> HPO <sub>4</sub> in 36% dioxane/ water	1.0	2.2	Stated only as u.v.	48
Syrup	0.3m x 4mm (i.d.) Waters µBondapak C18	0.05M KH <sub>2</sub> PO <sub>4</sub> in water containing 13% (v/v) methanol	2.0	3.0	254nm	49
Tablets, capsules, liquid	0.3m x 4mm (i.d.) Waters µBondapak phenyl	Water/methanol/acetic acid (55:44:1) con- taining 0.005M sodium heptane sulphonate	2.0	Not Stated	254nm	50
Tablets, liquid	0.3m x 4mm (i.d.) Waters µBondapak CN	13% acetonitrile in water containing 1.8% acetic acid 13% acetonitrile in water containing 1.8%	Gradient elution	7.5 8.8	254nm	51
		acetic acid and 0.005M sodium heptane sulphonate				
Tablets	0.25m x 4.6mm (i.d.) Whatman Partisil-10- ODS	2.85 x 10 <sup>-3</sup> M ethylene- diamine buffer (pH 7.44)/acetonitrile (1:1)	3.8	3.3	216.5nm	52

TABLE 3 (continued)						
Column	Mobile Phase	Flow rate (ml/min)	R <sub>T</sub> (mins)	Detection		
0.3m x 3.9mm (i.d.) Waters µBondapak C18	Methanol/water/acetic acid (45:54:1)	2.0	8.2	254nm		
0.3m x 3.9mm (i.d.) Waters µBondapak phenyl	Methanol/water (60:40) with 0.004M sodium heptane sulphonate and	1.0	7.4	254nm		
Waters µBondapak C18	1% acetic acid	1.0	11.7			
0.25m x 2mm (i.d.) Lichrosorb SI 100 and Wakogel LC 5H	Chloroform/ethyl acetate/ethanol/ n-hexane (25:10:1:50)	1.2	9.9	450nm		
LDC 5µ ODS	40% acetonitrile in water containing ammonium acetate and	1.8	8.2	Fluorescence detection		

0.3m x 3.9mm (i.d.) Acetonitrile/water Waters µBondapak C18 (25:75) with 0.005M sodium heptane sulphonate and 0.2% 1M HCL

acetic acid

0.1M KH\_PO4 in 10%

aqueous ethanol

0.15m x 4.6mm (i.d.) Syrup Spherisorb S5W

Drug

Source

Urine

Syrup

Urine

Plasma

Serum,

urine

1.3 4.8 220nm 57

Ref

-

53

54

55

56

5.4 198nm 58 1.0

# 7. Absorption, Disposition and Pharmacokinetics

Relatively little information has been reported on the metabolism of phenylpropanolamine hydrochloride. In urine studies with human subjects it was found that approximately 90% of the drug was excreted in 24 hours, predominantly unchanged (11, 60, 61). Sinsheimer et al. (60) found only 4% as transformation products, the major biotransformations being parahydroxylation to 4-hydroxynorephedrine and oxidative deamination of the side chain, resulting in hippuric acid. Phenylpropanolamine is also metabolised by phenylethanolamine-N-methyltransferase to the corresponding Nmethylated metabolite (62, 63). In the rat and rabbit, 80-90% of  ${}^{14}C$  of small oral doses of  $[{}^{14}C]$  norephedrine is excreted in the urine within 24 hours, with 1-2% of the dose being excreted in the faeces. In the rat, 60% occurs as the unchanged drug and 35% as 4-hydroxynorephedrine. Small amounts of 4-hydroxyhippuric acid and 1,2-dihydroxy-1-phenylpropane were also detected. In the rabbit however, 76% is excreted as deamination products consisting of 31% 1.2dihydroxy-1-phenylpropane, 27% 1-hydroxy-2-oxo-1-phenylpropane and 24% benzoic acid (60). In a study with human subjects under controlled conditions of urinary pH, acidification of the urine resulted in the excretion of largely unchanged phenylpropanolamine hydrochloride, whereas basic urine conditions resulted in reabsorption of the drug with little influence on metabolsim (64).

The mean elimination half-life of phenylpropanolamine hydrochloride in man has been reported as 3.9 hours and the elimination rate constant as 0.18 hr<sup>-1</sup> (11). After oral administration of phenylpropanolamine hydrochloride as an aqueous solution, absorption is rapid, being completed in less than 2.5 hours (64). The tissue distribution of the drug in dogs 2 hours after administration is kidney > lung > liver > spleen > brain > heart > muscle > plasma > fat > cerebrospinal fluid (65).

# 8. Identification and Determination in Biological Fluids

The isolation and quantitative determination of phenylpropanolamine from serum/plasma and urine has been accomplished by gas chromatography (34, 37, 39, 43) and high performance liquid chromatography (53, 55-57). Typical serum phenylpropanolamine concentrations after a single dose of 25 mg of the hydrochloride salt range from about 5-80 ng/ml over a period of 24 hours (56). In a more recent study using a 150 mg sustained-release tablet, serum and urine concentrations ranged from about 60-275 ng/ml and  $0.02-100 \ \mu$ g/ml respectively (57). Typical chromatograms depicting the high performance liquid chromatographic separation of the drug in serum and urine are shown in Figures 6 and 7 (57).

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(a) HPLC chromatogram of blank serum extract.

(b) HPLC chromatogram of serum extract containing phenylpropanolamine (1) and ephedrine (2).



- (a) HPLC chromatogram of blank urine extract.
- (b) HPLC chromatogram of urine extract containing phenylpropanolamine (1) and ephedrine (2).

#### REFERENCES

- 1. C. Mannich and W. Jacobsohn, Ber., 43, 189 (1910).
- P.R. Pentel, F.L. Mikell and J.H. Zavoral, Br. Heart J., 47, 51 (1982).
- H.I. Silverman, B.E. Kreger, G.P. Lewis, A. Karabelas, R. Paone and M. Foley, Curr. Ther. Res., 28, 185 (1980).
- J. Loman, M. Rinkel and A. Myerson, Am. Heart J., <u>18</u>, 89 (1939).
- B.M. Vanderbilt and H.B. Hass, Ind. Eng. Chem., <u>32</u>, 34 (1940).
- The Merck Index, Ninth ed., Merck and Co., Inc., Rahway, N.J., 1976, p. 950.
- H.E. Smith, E.P. Burrows, J.D. Miano, C.D. Mount,
  E. Sander-Bush and F. Sulser, J. Med. Chem., <u>17</u>, 416 (1974).
- A. Podder, J.K. Dattagupta and N.N. Saha, Indian J. Phys., <u>53A</u>, 652 (1979).
- 9. G.P. Lewis, Brit. J. Pharmacol., 9, 488 (1954).
- 10. L. Chafetz, J. Pharm. Sci., 52, 1193 (1963).
- K.R. Heimlich, D.R. Macdonnel, T.L. Flanagan and
  P.D. O'Brien, J. Pharm. Sci., 50, 232 (1961).
- N.H. Brown and G.A. Portmann, J. Pharm. Sci., <u>60</u>, 1229 (1971).
- 13. J.E. Wallace, J. Pharm. Sci., 58, 1489 (1969).
- F.A. Rotondaro, J. Assoc. Off. Agric. Chem., <u>41</u>, 509 (1958).
- D. Burke, V.S. Venturella and B.Z. Senkowski, J. Pharm. Sci., 63, 269 (1974).
- O.W.A. Weber and J.E. Heveran, J. Pharm. Sci., <u>62</u>, 1174 (1973).

- B.B. Shenoy and V. Das Gupta, J. Pharm. Sci., <u>62</u>, 802 (1973).
- 18. L.L. Shankle, J. Pharm. Sci., 67, 1635 (1978).
- J.A.F. de Silva and N. Strojny, Anal. Chem., <u>47</u>, 714 (1975).
- 20. A.W. Steers, J. Assoc. Off. Agric. Chem., 37, 683 (1954).
- M.C. Vincent, E. Krupski and L. Fischer, J. Am. Pharm. Assoc., 46, 85 (1957).
- 22. D.J. Smith, J. Assoc. Off. Anal. Chem., 53, 116 (1970).
- 23. D.J. Smith, J. Assoc. Off. Anal. Chem., 57, 741 (1974).
- 24. G. Smith, J. Assoc. Off. Agric. Chem., 41, 499 (1958).
- 25. D.J. Smith, J. Assoc. Off. Anal. Chem., 49, 536 (1966).
- 26. C.C. Clark, J. Assoc. Off. Anal. Chem., 56, 100 (1973).
- 27. H. Schriftman, J. Pharm. Sci., 55, 985 (1966).
- N.H. Brown and G.A. Portmann, J. Pharm. Sci., <u>60</u>, 1229 (1971).
- J.J. Shah and R.J. Shah, J. Assoc. Off. Anal. Chem., 59, 1416 (1976).
- 30. G. Gübitz, Chromatographia, 12, 779 (1979).
- R. Wintersteiger, G. Gübitz and A. Hartinger, Chromatographia, 13, 291 (1980).
- M.L. Bastos, D. Jukofsky and S.J. Mulé, J. Chromatog., 81, 93 (1973).
- A.H. Beckett, G.R. Jones and S. Al-Sarraj, J. Pharm. Pharmac., 26, 945 (1974).
- E. Appel, G. Planz, D. Palm, H. Grobecker, D. Stratmann and M. Donike, Europ. J. Clin. Pharmacol., 8, 161 (1975).
- C. Hishta and R.G. Louback, J. Pharm. Sci., <u>58</u>, 745 (1969).

- 36. E. Mario and L.G. Meehan, J. Pharm. Sci., 59, 538 (1970).
- L. Neelakantan and H.B. Kostenbauder, J. Pharm. Sci., 65, 740 (1976).
- R.E. Madsen and D.F. Magin, J. Pharm. Sci., <u>65</u>, 924 (1976).
- H. Kinsun, M.A. Moulin and E.C. Savini, J. Pharm. Sci., 67, 118 (1978).
- 40. B.R. Rader and E.S. Aranda, J. Pharm. Sci., <u>57</u>, 847, (1968).
- E. Brochmann-Hanssen and A.B. Svendsen, J. Pharm. Sci., 51, 938 (1962).
- P. Cancalon and J.D. Klingman, J. Chrom. Sci., <u>10</u>, 253 (1972).
- L.M. Cummins and M.J. Fourier, Anal. Lett., 2, 403 (1969).
- 44. D.E. Van Zwol, J. Chromatog., 24, 26 (1966).
- P.S. Doshi and D.J. Edwards, J. Chromatog., <u>176</u>, 359 (1979).
- 46. A.C. Celeste and M.V. Polito, J. Assoc. Off. Anal. Chem., 49, 541 (1966).
- 47. J.K. Baker, Anal. Chem., 49, 906 (1977).
- 48. T.L. Sprieck, J. Pharm. Sci., 63, 591 (1974).
- 49. V. Das Gupta and A.G. Ghanekar, J. Pharm. Sci., <u>66</u>, 895 (1977).
- T.R. Koziol, J.T. Jacob and R.G. Achari, J. Pharm. Sci., 68, 1135 (1979).
- A.G. Ghanekar and V. Das Gupta, J. Pharm. Sci., <u>67</u>, 873 (1978).
- 52. D.R. Heidemann, J. Pharm. Sci., 70, 820 (1981).
- 53. F.T. Noggle Jr., J. Assoc. Off. Anal. Chem., <u>63</u>, 702 (1980).

- 54. N. Muhammad and J.A. Bodnar, J. Liq. Chrom., <u>3</u>, 113 (1980).
- M. Endo, H. Imamichi, M. Moriyasu and Y. Hashimoto, J. Chromatog., 196, 334 (1980).
- W.D. Mason and E.N. Amick, J. Pharm. Sci., <u>70</u>, 707 (1981).
- 57. R. Dowse, J.M. Haigh and I. Kanfer, J. Pharm. Sci., <u>72</u>, (1983) in press.
- G.B. Cox, C.R. Loscombe and K. Sugden, Anal. Chim. Acta, 92, 345 (1977).
- R.H. Barry, M. Weiss, J.P. Johnson and E. De Ritter, J. Pharm. Sci., 71, 116 (1982).
- J.E. Sinsheimer, L.G. Dring and R.T. Williams, Biochem. J., 136, 763 (1973).
- A.H. Beckett and G.R. Wilkinson, J. Pharm. Pharmac., <u>17</u>, 107S (1965).
- 62. M.E. Wolfe, "Burger's Medicinal Chemistry", John Wiley and Sons Inc. (Canada), 4th Ed., Part 1, 1980, p. 202.
- B. Testa and P. Jenner, "Drug Metabolism : Chemical and Biochemical Aspects", Marcel Dekker Inc. (New York), 1976, p. 314.
- 64. G.R. Wilkinson and A.H. Beckett, J. Pharmacol. Expt. Ther., 162, 139 (1968).
- 65. J. Axelrod, J. Pharmacol. Expt. Therap., 109, 62 (1953).

This profile attempts to cover the published literature on phenylpropanolamine hydrochloride up to July 1982.