TRIMIPRAMINE MALEATE

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1. Description

1.1 Nomenclature

1.11 Chemical Names

- 10,11-Dihydro-N,N,β-trimethyl-5H-dibenz[b,f] azepine-5-propanamine hydrogen maleate
- 5-[3-(Dimethylamino)-2-methylpropyl]-10,11-dihydro-5H-dibenz[b,f]azepine hydrogen maleate
- 5-(3-Dimethylamino-2-methylpropy)iminodibenzyl hydrogen maleate
- 3-(10-11-Dihydro-5H-dibenz[b,f]azepine-5-yl) -2-methyl-propyl-N,N-dimethyl ammonium hydro -gen maleate
- 5-(3-Dimethylamino-2-methylpropy)-10,11-dihydro-5H-dibenz[b,f]azepine hydrogen maleate
- Trimipramine acid maleate
- Trimipramine hydrogen maleate

1.12 Generic Names

Trimepramine, Trimeprimine, Trimeproprimine RP 7162, Sapilent.

1.12 Trade Names

Stangyl, Surmontil

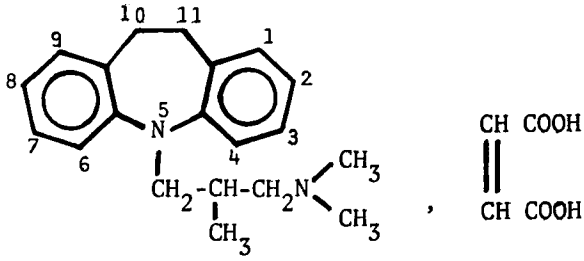
1.2 Formulae

1.21 Impirical

$C_{20}H_{26}N_2$ (base)

$C_{20}H_{26}N_2$, $C_4H_4O_4$ (maleate salt)

1.22 Structural



1.3 Molecular Weight

Trimipramine	294.42
Trimipramine maleate	410.5

1.4 Elemental Composition

C	81.58%	H	8.90%	N	9.52%			(base)
C	70.22%	H	7.36%	N	6.82%	O	15.60%	(maleate)

1.5 Chemical Abstract Registry Number

[739-71-9] base
[521-78-8] maleate salt

1.6 Appearance, Color and Odor

A white crystalline, powder, odorless or almost odorless (1).

2. Physical Properties

2.1 Melting Point

Trimipramine	45°	(2)
Trimipramine maleate	140-144°	(1)

2.2 Solubility

Trimipramine maleate is slightly soluble in water and in ethanol (96%); freely soluble in chloroform; practically insoluble in ether (1).

2.3 Identification

Clarke (2) described the following tests:

I) Trimipramine can be identified by forming crystals with platinic chloride solution where needles, often serrated are formed (sensitivity: 1 in 1000). Trimipramine also forms dense rosettes with trinitrobenzoic acid solution (sensitivity 1 in 1000).

II) Trimipramine can be identified by the following color tests:

- Ammonium molybdate test; blue color is produced (sensitivity 0.1 µg).
- Ammonium vanadate test; blue color is produced (sensitivity 0.1 µg).
- Vitali's test; deep green/yellow/yellow (sensitivity 0.1 µg).

The following tests are cited in both European Pharmacopoeia 1975 (3) and the B.P. 1980 (1) for the identification of trimipramine maleate:

a) To 0.1 g add 2 ml of alcohol, heat to boiling and add 1 ml of a standard solution of picric acid in alcohol. Scratch the walls of the tube with a glass rod until crystallization begins. Allow to stand for 15 minutes, filter, wash the precipitate with alcohol and dry at 100° to 105°. The picrate has a melting point of 131°.

b) Triturate 0.1 g with 3 ml of water and 1 ml of strong sodium hydroxide solution and extract with three quantities, each of 5 ml of ether. To the aqueous solution add 2 ml of bromine solution. Heat in a water bath for 10 minutes, then heat to boiling and cool. Add to 0.1 ml of this solution, a solution of 10 mg of resorcinol in 3 ml of sulphuric acid and heat on a water bath for 2 minutes, then cool. A deep blue color develops.

c) A 0.002 per cent w/v solution in 0.1 N hydrochloric acid, examined between 230 nm and 350 nm, shows a single absorption maximum at about 250 nm. The extinction at the maximum at about 250 nm in a 1 cm cell is about 0.42.

The following test is cited in the European Pharmacopoeia 1975 (3).

Dissolve about 5 mg in 2 ml of nitric acid; an intense blue color is produced which turns green on standing.

2.4 Spectral Properties

2.41 Ultraviolet Spectrum

The ultraviolet spectrum of trimipramine maleate in neutral methanol solution in the region of 200 to 350 nm exhibits a maximum at 247 nm and a minimum at 233 nm. The spectrum is shown in Figure 1.

Trimipramine in 0.1 N sulphuric acid exhibited a maximum at 250 nm ($E_{1\%}$, 1 cm 300) and an inflexion at about 268 nm ($E_{1\%}$, 1 cm 250) (2).

According to B.P. 1980 (2) the UV spectrum of trimipramine maleate of a 1 cm layer of 0.002 percent w/v solution in 0.1 M HCl exhibits a maximum only at 250 nm and an absorbance at 250 nm, about 0.42.

2.42 Infrared Spectrum

The infrared spectrum of trimipramine maleate is shown in Figure 2. The spectrum was obtained as KBr disc. The structural assignments have been correlated with the following band frequencies:

Frequency (cm^{-1})	Assignment
3430	$N\text{-}CH_3$
3057	Aromatic CH stretch
2949, 2825	Asymmetric and Symmetric CH stretch

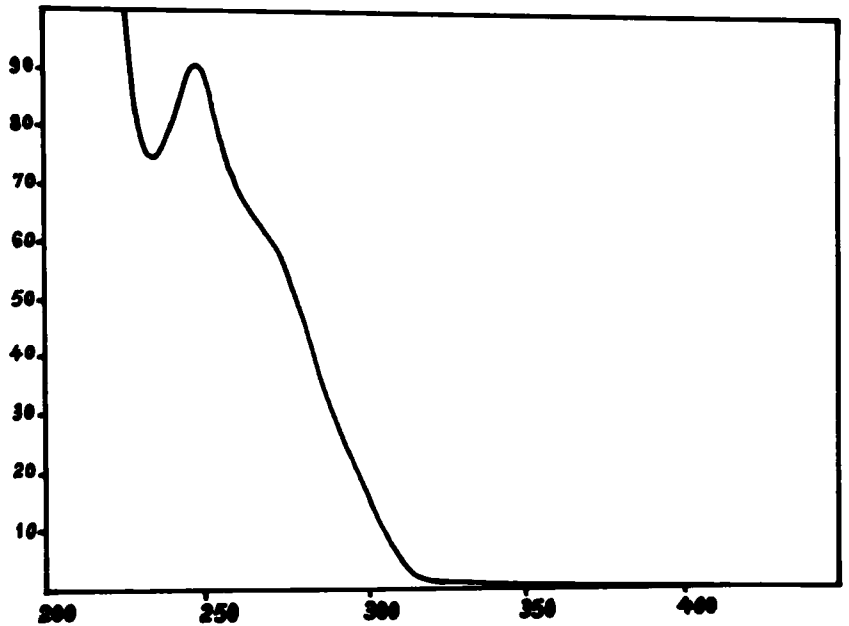


Figure 1: Ultraviolet Spectrum of Trimimpramine maleate in neutral methanol.

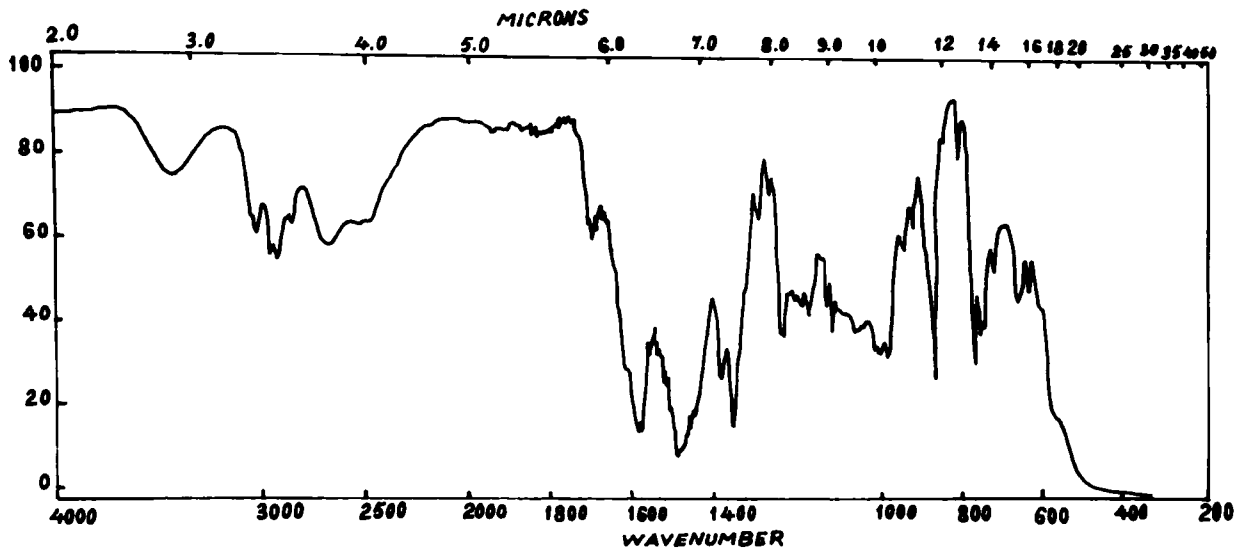


Figure 2: Infrared Spectrum of Trimipramine maleate: KBr disc.

2921, 2852	Asymmetric and Symmetric CH_2 stretch.
1620, 1570	Aromatic C=C stretch.

Other finger print band characteristics to trimipramine (determined in KBr disc) are 1351, 1488 and 1580 cm^{-1} (2).

2.43 Proton Nuclear Magnetic Resonance Spectrum (PMR)

The 60 MHz spectrum of trimipramine maleate in deuterated dimethylsulphoxide is shown in Figure 3. The spectrum was determined in Varian T60 A NMR Spectrometer with tetramethylsilane (TMS) as reference standard. Assignment of the bands are as follows:

Chemical shift ppm	Multiplicity	Assignment
0.98	d	CH_2-CH($\underline{CH_3}$)-CH_2-
2.8	s	-N($\underline{CH_3}$)($\underline{CH_3}$)
3.1-3.9 (unresolved)	m	Methylene protons.
6.15	s	CH=CH (maleate)
7.05	m	Aromatic protons.

s: singlet; d: doublet; m: multiplet.

Proton magnetic resonance was reported to be useful for the identification of trimipramine and some other tricyclic psychotropic drugs. The drug can be characterized by examining the signal given by the protons of the ring and side chain. It is also reported that NMR spectrometry is a technique of choice for the rapid identification of the drug (4).

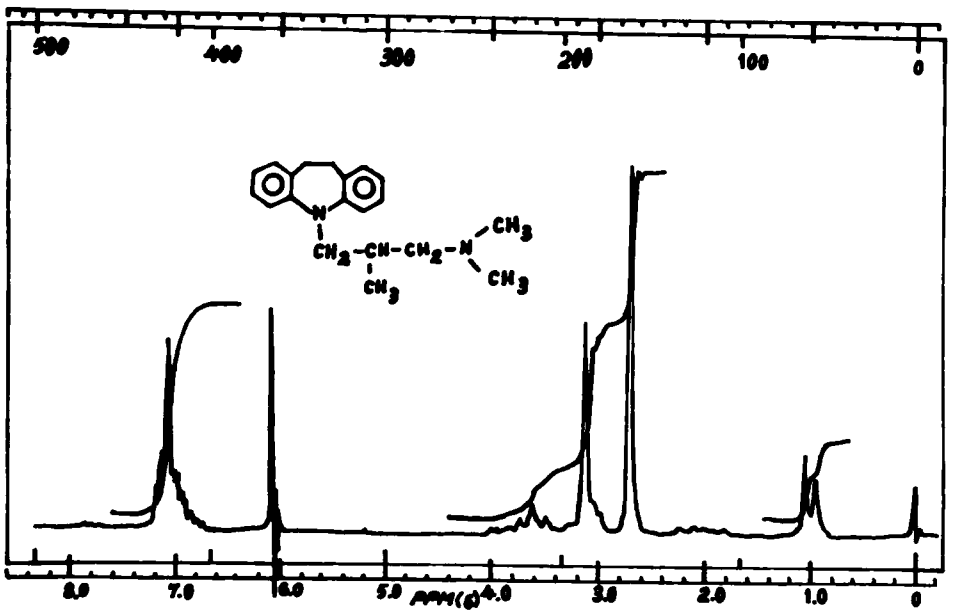


Figure 3: PMR Spectrum of Trimipramine maleate in DMSO-D_6 with TMS as internal standard.

2.44 ^{13}C-Nuclear Magnetic Resonance Spectrum (^{13}C NMR)

The ^{13}C-NMR spectrum of trimipramine maleate in deutrated chloroform using tetramethylsilane as an internal reference is obtained on a Jeol FX 100-100 MHz at an ambient temperature using 10 mm sample tube. The spectrum is shown on Figure 4 and the carbon chemical shift values, shown in Table 1 are derived from the off-resonance spectrum.

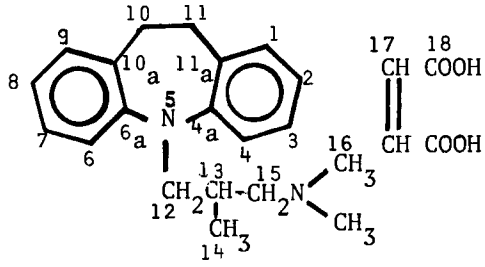


Table (1) ^{13}C-NMR characteristics of trimipramine maleate

Carbon No.	Chemical Shift (ppm)	Carbon No.	Chemical Shift (ppm)
1	126.96	11	32.06
9	126.96	10_a	133.81
2	119.48	11_a	133.81
8	119.48	12	54.38
3	130.12	13	27.68
7	130.12	14	16.76
4	135.56	15	62.47
6	135.56	16	43.27
4_a	147.45	17	123.19
6_a	147.45	18	169.27
10	32.06		

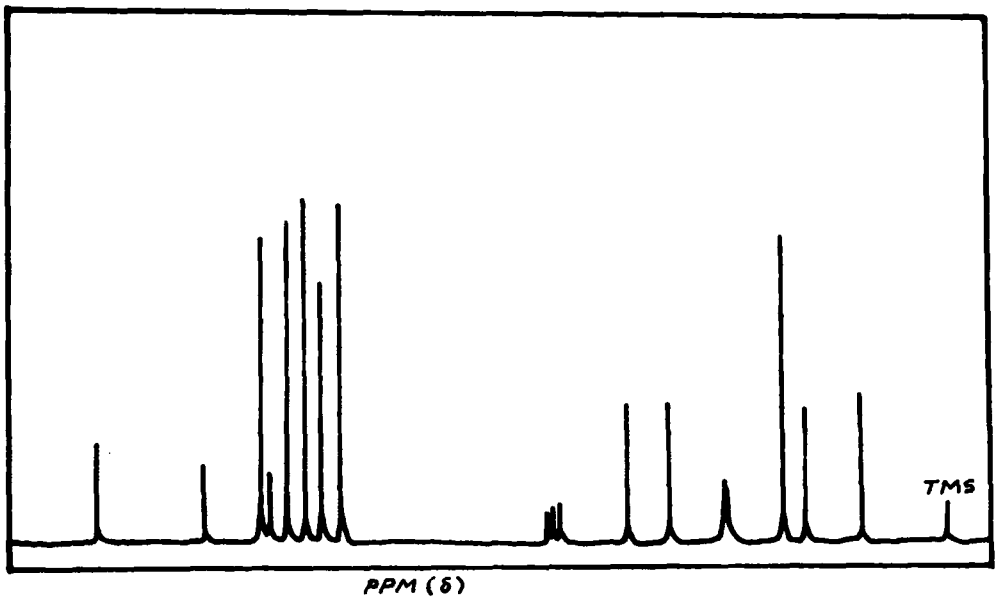
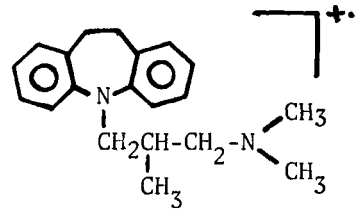
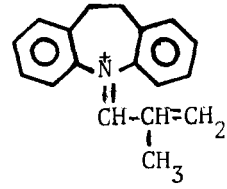
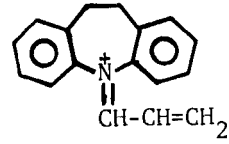
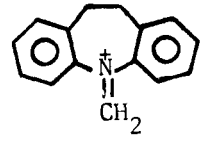
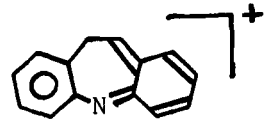


Figure 4: Carbon-13 NMR Spectrum of Trimipramine maleate in $CDCl_3$ with TMS as internal reference.

2.45 Mass Spectrum and Fragmentometry

The mass spectrum of trimipramine maleate (Figure 5) obtained by electron impact ionisation, using Finnigan mass spectrometer shows a molecular ion $M^{+\cdot}$ at m/e 294 (relative intensity 25%). Table (2) shows the proposed fragmentation of trimipramine.

Table (2) Proposed fragmentation of trimipramine(EI)

m/e	Relative intensity %	ion
294	25	
249	100	
234	35	
208	50	
193	70	

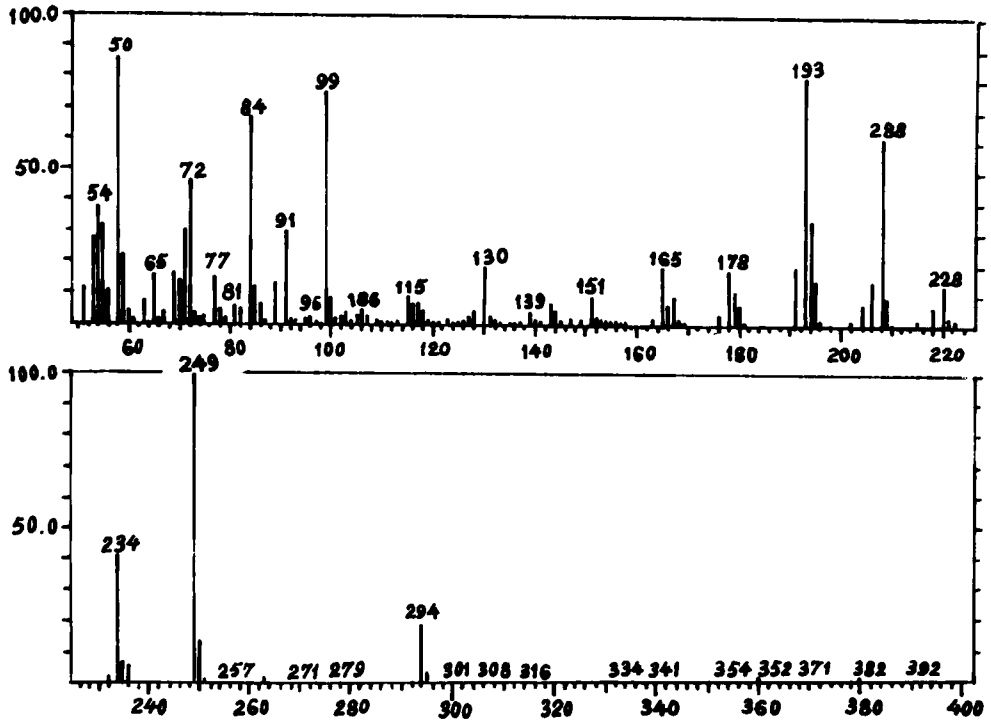
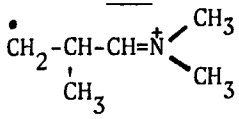
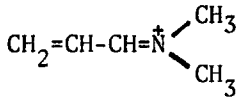
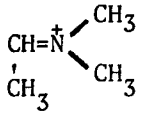
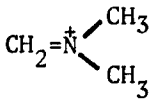


Fig. 5. Mass Spectrum of Trimipramine maleate (EI).

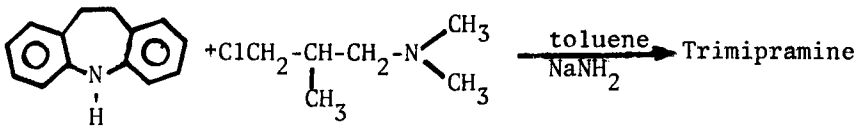
m/e	Relative intensity %	ion
99	65	
84	63	
72	32	
58	82	

Cailleux and Allain (5) reported that chemical ionisation was superior to electron impact for identification of four drugs including trimipramine, by gas-chromatography-mass spectrometry. The drugs cannot be separated by GLC at 220° on an SE 30-Chromosob column, nor can they be unequivocally distinguished by electron-impact mass spectrometry. Spectra are reproduced to show that these drugs can be clearly distinguished by chemical ionisation-mass spectrometry with CH_4 as reagent gas.

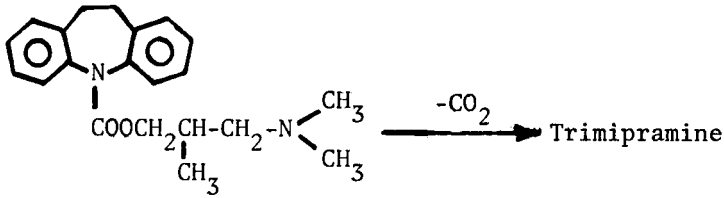
3. Synthesis

Trimipramine can be synthesized by the following methods:

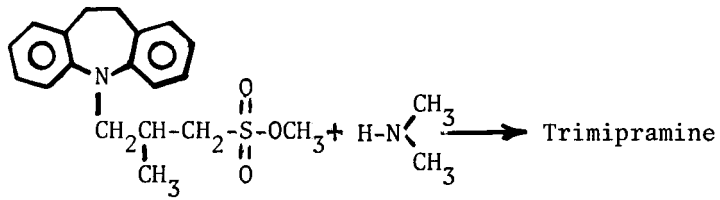
a) Condensation of 10,11-dihydro-5H-dibenz[b,f] azepine and $(CH_3)_2NCH_2CH(CH_3)CH_2Cl$ in toluene with sodamide (6) (7)



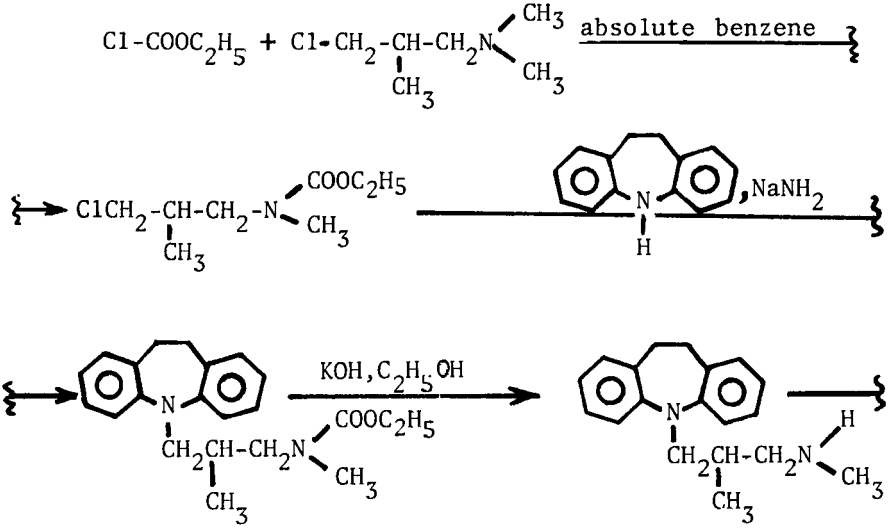
b) Decarboxylation of the 5-[$(CH_3)_2NCH_2CH(CH_3)CH_2OCO$] derivative of 10,11-dihydro-5H-dibenz [b,f]azepine(6)

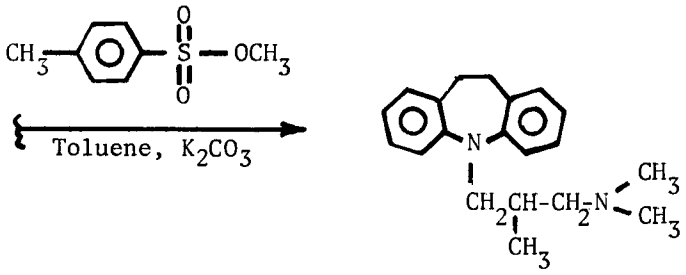


c) Reaction of the 5-[CH_3SO_3 $CH_2CH(CH_3)CH_2$] derivative of 10,11-dihydro-5H-dibenz[b,f] azepine with dimethylamine (6).

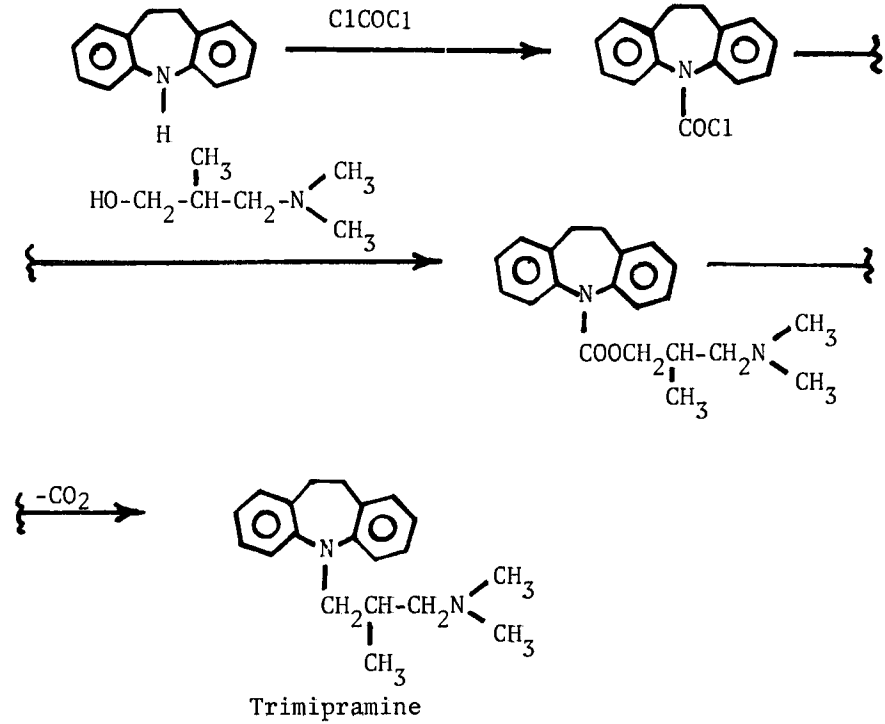


d) By the general method described by Budai et al (8) according to the following scheme:





e) 10,11-Dihydro 5H-dibenz [b,f] azepine was converted to its 5-COCl derivative by the reaction with phosgene. This product was allowed to react with $HOCH_2CH(CH_3)CH_2-N(CH_3)_2$ to form 5-(3-dimethylamino-2-methylcarboxylate) intermediate. The latter is decarboxylated to give trimipramine (9).



Trimipramine

4. Metabolism and Excretion

Studies on rabbits and dogs have shown that trimipramine is extinsively metabolized (2). Populaire et al (10) reported that, after oral ingestion of trimipramine, both the drug and its monodemethylated derivative were found in the circulating blood of dogs and rabbits; the concentration in the blood were low, and maximum concentrations were reached within the first 6 hours. Within 72 hours, dogs excreted 1.5-8% of the ingested dose, (50-70% in the conjugated form), in the urine and 2-25% in the feces; the corresponding values in rabbit were 10-20% (90%) and <2% respectively. At least 26 metabolites were detected in the excreta. The metabolism of trimipramine in humans and animals appeared to be similar.

5. Methods of Analysis

5.1 Titrimetric Methods

a) Aqueous Titration

Potassium hexathiocyanatochromate $K_3Cr(SCN)_6$ was used (11) in the determination of trimipramine. The reagent precipitated trimipramine base (HB) as $Cr(SCN)_6$ H_3-3B and the excess reagent was titrated with $KBrO_3$. The method was suitable for analysing 6-20 mg samples with relative deviation of 0.2-0.8%.

b) Non-Aqueous Titration

B.P. 1980 (1) and European Pharmacopoeia 1975 (3) determined trimipramine by the non-aqueous titration with 0.1 N perchloric acid using crystal violet solution as an indicator.

c) Oscillometric Titration

Pomazanska - Kolodziejska (12) reported the use of an oscillometric method for titration of trimipramine among other related pharmaceutical compounds with HCl in acetone/ethanol solution.

5.2 Spectrophotometric Methods

5.21 Nuclear Magnetic Resonance Spectroscopy

A new method was described (13) for the assay of trimipramine maleate and its base using ^1H NMR technique. The method employed is precise, accurate, rapid and helpful in qualitative identification and purity of the drug.

5.22 Fluorescence-Phosphoresence

Trimipramine, among other dibenzazepines, gave with $KMnO_4$, a green fluoresence which can be used for analytical purpose (14) with a sensitivity of >0.06-0.1 γ/ml.

Gifford et al (15) studied the luminesence characteristics of trimipramine and several classes of drugs affecting the central nervous system. The compound was studied in ethanol at at 77K. The characteristics for trimipramine are:

Excitation maxima 300 nm, the phosphoresence maxima 450-470 nm and the phosphoresence life time 0.70 sec.

5.23 Colorimetric Methods

a) French et al (16) reported a colorimetric analysis of some dibenzazepines including trimipramine. The determination of these drugs has been studied by:

1. Treatment in acid solution with HNO_2 and measurement of the extinction of the reaction mixture at 390 nm.

2. Addition of bromothymol blue to solution buffered at pH 7 and extraction with benzene, with measurement of the extinction of the benzene extract at 410 nm.

3. Direct measurement of the extinction of the acid solution at 251 nm. The analysis

by the three methods was used for the assays of tablets and injections. Although all the three methods have essentially the same accuracy and precision for bulk drugs, the colorimetric procedures are less subject to interfere by other material (e.g. U.V. absorbers) that may be present in pharmaceutical preparation.

b) Slunjski and Turkovic (17) reported that the reaction between 32% HNO_3 and trimipramine produces a blue color which, after several minutes, changes to yellow. After evaporating off the solution to dryness on a water bath, dissolution of the residue in alcoholic KOH produces a stable red violet color exhibiting maximum absorption at 560 nm. The reaction can be used to determine 0.3 to 1.2 mg of drug in dragees or down to 1 ppm of the drug or its metabolites in urine, and is specific for compounds of this structure (e.g. imipramine, desipramine and trimipramine).

c) Klinge and Beyer (18) reported a simple method for detection and determination of trimipramine and its derivatives in chemical toxicology. The drug is extracted from blood, urine or body tissue extract into chloroform in the presence of Na_2CO_3. After evaporation of chloroform, the residue is dissolved in warm 80% acetic acid (5 ml) and the solution is diluted to 10 ml with 80% acetic acid. The drug is determined by heating 5 ml of the solution with one drop of fresh 2% $NaNO_2$ solution in a boiling water-bath for 10 min and measuring the extinction of the stable yellow color at 415 to 420 nm.

5.24 Atomic Absorption

Trimipramine, among other azepine bases, has been microdetermined by atomic absorption (19). The sensitivity of the method is 1-4 X 10^{-4}M. The method involves the formation of an ionic complex between the drug and sodium dioctyl sulfosuccinate (DOSS). After the pH of the reaction medium is adjusted to protonate the drug, known

amount of DOSS is added to form an ionic complex with the drug. If the complex is sufficiently stable, the excess DOSS is complexed with Cu o-phenathroline. The latter complex is extracted with methyl isobutyl ketone and the Cu concentration is determined by atomic absorption, if DOSS-drug complex has low stability, it may be removed by extracting with CCl_4 and the excess DOSS is then determined as described above.

5.3 Polarographic Method

Volke et al (20) used a 3-electrode polarograph, with a rotating-disc indicator electrode (≈1300 rpm) and s.c.e., for the attempted anodic oxidation, of trimipramine and other related compounds. Acetonitrile media were used, with 0.1 M tetrabutylammonium perchlorate as supporting electrolyte. At both platinum and gold indicator electrodes.

5.4 Chromatographic Methods

5.41 Gas-Chromatography

Clarke (2) reported the retention time of trimipramine to be 0.64 relative to codeine using 2.5% SE-30 on 80-100 mesh chromosob W A WHMDS, 5 feet X 4 mm id glass column.

Clarke (2) also reported a retention times of trimipramine to be 0.30 (0.15) relative to codeine using 3% XE-60 silicon nitrile polymer on 100-120 mesh chromosob W.

Viala et al (21) described a gas chromatographic technique for the identification of trimipramine using two types of columns, XE-60/ Igapal or Aeropack and UNCON polar or prealkalanized varport-30. The latter has the base or the salt of the compound in methanolic solution.

A rapid method is given (22) for the extraction and identification of trimipramine and some other basic drugs as well as their metabolites in urine. Gas-Chromatography, (glass coil packed with 3% OV-17 on gas-chrom Q 100-120

mesh, N carrier, flame ionization detector), was used as the primary source of identification.

5.42 Gas-Liquid Chromatography

Trimipramine was determined, among other tricyclic antidepressants, in biological fluids and tissues, by gas-liquid chromatography:

a) Reite (23) published a gas-liquid chromatography method for the determination of trimipramine and its main metabolite (monodesmethyltrimipramine) in human serum using nitrogen detection. The drug and its main metabolite were extracted from the serum with hexane and the metabolite was derivatized with trifluoroacetic anhydride.

b) Dawling and Braithwaite (24) reported a simplified method for monitoring trimipramine among some tricyclic antidepressant therapy using gas-liquid chromatography with nitrogen detection. The column was silanized glass packed with 3% SP 2250 on supelcoport, carrier gas was Ar, and the internal standard was maprotiline-HCl.

c) The pharmacokinetic characteristics, of two different formulations (capsule and tablets) of trimipramine, were determined with a new gas-liquid chromatographic method (25). Plasma plus amidopyrine (internal standard) is mixed with 10 M NaOH and extracted with hexane; the separated organic phase is dried and evaporated at 60° under nitrogen. A solution of the residue in ethyl acetate is analyzed by GLC on a solumn (6 ft X 2 mm) of Gas Chrom-Q(80-100 mesh) supporting 3% of OV-17, with nitrogen ionisation detection. After 9.5 min at 225° the column temperature is increased to 275° (maintained for 5.5 min) in 2 min; retention times are 4.05 min for amidopyrine and 8.15 min for trimipramine.

5.43 Column Liquid Chromatography

Van den Berg (26) described a column liquid chromatography system for the analysis of tri-

cyclic antidepressants including trimipramine. A high separation efficiency can be obtained with a mixture of ethyl acetate, n-hexane, and methylamine as eluent on a silica gel column. The retention is easily regulated by varying the concentration of n-hexane, the modifier methylamine, and the H_2O content of the ethyl acetate. Ultraviolet detection permits determination down to the 10-ng level in the serum.

5.44 Paper Chromatography

Clarke (2) described a solvent system consisting of citric acid: H_2O :n-butanol (4.8 gm: 130 ml : 870 ml). The system may be used for several weeks, if water is added from time to time to keep the specific gravity at 0.843 to 0.844. Trimipramine gives an R_f value of 0.73. The spots can be located under ultraviolet light, blue fluorescence. Iodoplatinate spray and bromocresol green spray were used as strong and weak location reagents respectively.

5.45 High-Pressure Liquid Chromatography

Trimipramine, among other tricyclic antidepressant was separated by high performance liquid chromatography on silica gel column using an eluting solvent of dichloromethane n-hexane (1:1) to which 0.2% of isopropyl alcohol and 0.13% of propylamine were added (27).

De Zeeuw et al (28) described a relatively simple and rapid procedures for the toxicological analysis of some commonly used tricyclic antidepressants including trimipramine. The methodology consisted of a single extraction from aqueous media at pH 10 with hexane followed by high-performance liquid chromatography (HPLC) on silica gel using straight phase system.

Uges and Bouma (29) determined trimipramine and its metabolites in serum by straight phase HPLC. The drug was separated from solution or from serum by HPLC on a column of silica gel, using CH_2Cl_2:CH_3OH: buffer pH 3.2 (90:10:0.15) as the mobile phase. The internal standard was proma-

zine-HCl and the compound was extracted from serum with CH_2Cl_2 under basic condition.

Alary and Villet (30) separated trimipramine by dichotomic extraction as a function of solvent polarity and pH and identified it by high-performance thin-layer chromatography and liquid chromatograph trimipramine was isolated by extraction with hexane in an alkaline medium (pH > 12). Cyclohexane:ethanol:butanol-25% NH_4OH (80:20:10:1) was used as the solvent in TLC. Cyclohexane:ethanol:diethylamine (80:20:10 :0.25) was used as the solvent in high pressure liquid chromatography.

Villet et al (31) reported a chromatographic method for separation of trimipramine among some psychotropic agents. The drug was separated by a micro thin-layer chromatography method and a high-performance liquid chromatography method (Si 60 column, cyclohexane:ethanol:butanol:NHOH 25% (80:20:10:0.4) at 1.75 ml/mm transposed from the first method. The high performance liquid chromatography method has the advantage of simultaneous separation, identification and quantitation.

Table (3) shows various high pressure chromatography systems used for the analysis of trimipramine in biological fluids.

5.46 Thin-Layer Chromatography

Several thin-layer chromatography methods for the separation and analysis of trimipramine have been described in the literature.

Macek and Vecerkova (35) reported a new method for identifying 161 medicinals including trimipramine. The method involves separation of substances into groups by extraction first at a low pH, and at a high pH, and then using an ion exchanger. The further separation is then done with paper chromatography, with thin-layer chromatography also serving for identification of the individual compounds.

Table (3) High-pressure Chromatography Systems

Column	Mobile Phase	Flow rate	Detector	Remarks	Ref.
20 cm X 4.6 mm Partisil 5 (mean Particle size 6 μm)	Methanol:2M-NH_3: 1 M-NH_4NO_3(27:2:1)	1 ml/min^{-1}	UV 254 nm	can be applied to the analysis of the drug and amitryptyline and to their metabolites in gastric fluids, blood and liver.	(32)
30 cm X 4.4 mm column packed with μ Bonda-pack C_{18}	35% acetonitrile in 45 mm KH_2PO_4 adjusted to pH 3.0 with phosphoric acid.	1.5 ml/min^{-1}	UV 235 nm	Retention time of the drug 11.8 min. The method is described to determine subtherapeutic to overdose level of the drug. Applied to other tricyclic antidepressant.	(33)
Octadecylsilane -coated spherisorb.	Methanol : H_2O (35 : 65)	1 ml/min^{-1}	Fluorescence spectrometer.	The retention volume from a point of injection for a 25 cm column with 3.7 l. The λf (fluorescence wavelength) = 412 mm	(34)

Clarke (2) described a solvent system consisting of strong ammonia solution; methanol (1.5:100). The system should be changed after two runs. Trimipramine gives an R_f value of 0.58. The chromatogram is visualized by acidified iodoplatinate spray.

Groningsson and Schill (36) described a thin-layer chromatography of trimipramine as an ion pair with Cl^-, Br^-, SCN^- and ClO_4^- as the counter ions in the aqueous phase. The stationary phase was a cellulose powder impegnated with the solution containing the counter ion. The mobile phases are chloroform, cyclohexane + 1-pentanol (7:3), cyclohexane + 1-pentanol (1:1). The visualization was made using Rhodamine B and Iodine.

Table (4) show other thin-layer chromatography systems.

5.47 Thin-Layer Chromatography-Mass Spectrometry

Combined thin-layer chromatography-mass spectrometry technique was applied for the analysis of trimipramine (37). Thin-layer chromatography was carried out on glass plates coated with GF_{254} silica gel. The drug was applied to the plates from the stand. solvent. The solvent system consists of acetic acid:ethanol:water (30:50:20). The silica gel containing the drug was removed from the plate and inserted into the mass spectrometer. The highest m/e in mass spectrum of TLC sample was m/e 294.

Table (4) Thin-layer chromatography systems for trimipramine analysis

Stationary Phase	Developing Solvent	Detecting Agent	Remarks	R_f value	Ref.
Silica gel G	Acetone: methanol: NH_4OH 50: 50 : 1	Alc. HNO_3		0.54	(38)
Silica gel G (activated)	Dehydrated peroxide-free ether: acetone:diethylamine (90:10:1) Benzene:acetone (100:20) shaken with 10 ml of 5% aq. NH_3 solution.	Spraying with dil. iodo-platinate reagent in N-HCl followed by 50% H_2SO_4 and examining under U.V. radiation.	Fluorescence can be performed after 24 hours. Positive results are obtained with 100 mg of the product.	0.170 0.154	(39)
Kieselgel G	1) Methanol:acetone (12:88) 2) Ethanol:tetrachloroethane (16:84) 3) Methanol:benzene (31.7:68.3) 4) Ethanol:toluene (68:32) 5) Methanol:cyclohexane:ethyl acetate (17.8:33.6:48.6)	UV light (254 mm after spray with Dragendorff's reagent).		0.4 0.8 0.65 0.5 0.64	(40)

Contd....

Stationary	Developing Solvent	Detecting Agent	Remarks	R_f value	Ref.
Silica gel G	Hexane:anhydrous diethylamine (93:7)	85% H_3PO_3 saturated with $KClO_4$ and heat.	It is possible to identify a psychotropic drug in urine in the event of toxicological emergency.	-	(41)
Kieselgel GF_{254}	-Ether:acetone:ethyl acetate: diethylamine (85:11:2:2) -Benzene:acetone:diethylamine (50 : 10 : 5) -Methanol:cyclohexane:Methyl acetate (17.8:33.6:48.6) -Butanol:toluene:methanol: H_2O : acetic acid (22:48:18:7:5)	Iodine vapour Bromine vapour	Used for rapid identification. Used for rapid identification. Used for the identification of the tertiary amine.	- - -	(42)
Kieselgel $60F_{254}$	Cyclohexane:ethanol:butanol: 25% NH_4OH (80:20:10:0.4)	-	-	0.61	(31)
Kieselgel GF_{254}	Methanol:25% aq.NH_3 (100 : 1)	-UV radiation -Spray with 5% $NaNO_2$ soln. in 80% methanol.	-	-	(18)

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