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PROGRAMME ON

SUBSTANCE ABUSE

Information Manual on Designer Drugs

An information booklet on new types of drugs of abuse – analogues of controlled substances

WORLD HEALTH ORGANIZATION

PREFACE

Psychoactive drugs have been part of human life since ancient times. First, drugs of natural origin or "vegetable" drugs such as opium, cannabis and coca leaves were used. During the first half of the 20th century "classical" synthetic drugs such as pethidine, methadone, LSD, amfetamines and depressants were added. Most of these drugs were placed under international control under either the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971.

Since the late 1970s, new types of synthetic drugs have emerged. They are similar to controlled substances in chemical structure and pharmacological activity, but different enough to avoid legal control applicable to the "mother" compounds. These analogues of controlled substances are often referred to as "designer drugs", because they are "designed" by chemists in clandestine laboratories in an attempt to circumvent drug control laws.

Some of these designer drugs are extremely potent, and have claimed many lives in overdose cases. Some can cause serious damage to the brain function. When the risk they present to the health of individuals and society was documented, the United Nations Commission on Narcotic Drugs, based on recommendations by WHO, decided to place them under international control. Therefore, many of the known designer drugs are no longer "controlled substance analogues" since they have become controlled substances themselves.

The abuse of designer drugs was virtually confined to the United States of America throughout most of the last decade. In the late 1980s, however, there were indications that some of them were beginning to reach Europe and Asia. At the meeting on clandestinely produced drugs held in Rabat, Morocco in 1987, it was recommended that an information manual on designer drugs be made available to national health and forensic laboratory personnel, so that they would be better prepared to face the problem, should these drugs begin to spread in other countries.

This manual has been prepared to respond to the above recommendation with the financial support of the United Nations Fund for Drug Abuse Control (UNFDAC, which recently became an element of the United Nations Drug Control Programme) in collaboration with the group of scientists listed on the following page. Their contribution to the designing, drafting and editing of the manual is cordially acknowledged.

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INTRODUCTION

The manual is intended for use by health and forensic laboratory personnel as a source of information on "designer drugs". Health ministry officials may find the general information in the manual useful to be better prepared for the eventuality of these drugs appearing in the national drug abuse scene. Hospital staff will find the pharmacological and clinical information useful when they come across a patient intoxicated with an unknown drug. Forensic chemists may use the chemical and analytical information as a practical guide for laboratory testing of these substances should they be encountered in the illicit traffic.

This manual is divided into five chapters - two on analogues of fentanyl and meperidine controlled under the Single Convention on Narcotic Drugs, followed by three chapters on analogues of amfetamines, phencyclidine and aminorex controlled under the Convention on Psychotropic Substances. Each chapter begins with a general statement of the problem followed by a section describing the general history of the group of drugs in question. Then, pharmacologic and toxicological information is given, followed by a section on clandestine synthesis and analytical chemistry intended mainly for forensic chemists. At the end of this section, data sheets of individual substances are provided.

In the data sheets, information on international control is provided in abbreviation; the number of the Schedule containing the substance followed by the abbreviated name of the convention. For example, "I, 1961 Convention" means that the substance is included in Schedule I of the Single Convention on Narcotic Drugs, 1961. "1971 Convention" refers to the Convention on Psychotropic Substances, 1971. In composite drug names containing both chemical prefixes and INNs (International Non-proprietary Names), the INN is often distinguished by being italicized or underlined. This method of distinguishing INNs in composite drug names was not employed in this manual.

References are given at the end of each chapter under two headings: general and chemistry. General references are those which are used but not cited in the text. In the analytical chemistry section, however, all references listed under the chemistry reference heading are cited so that the original papers can be readily identified when more details are needed.

Even with detailed information on experimental conditions and substance data sheets, actual confirmatory testing may not be possible without the use of a reference standard of the drug in question. Should the need arise, more information about the possible source of reference standards is available from either the Narcotics Laboratory of the United Nations Drug Control Programme or the Special Testing and Research Laboratory of the Drug Enforcement Administration of the United States of America.

The substances in this manual represent only some of the analogues which have been encountered in the illicit traffic. Analytical chemistry data on other similar analogues are available from the following sources: CND Analytical, Inc., P.O. Box 1527, Auburn, Alabama 36831-1527, USA; United States Drug Enforcement Administration Special Testing and Research Laboratory, McLean, Virginia 22101, USA; and Narcotics Laboratory, UN Drug Control Programme, Vienna International Centre, P.O. Box 500, A-1400 Vienna, Austria.

FENTANYL ANALOGUES

GENERAL STATEMENT OF THE PROBLEM

Fentanyl and its analogues are a class of designer drugs which have been synthesized in clandestine laboratories using common, commercially available chemicals and simple laboratory equipment. The biological effects of the fentanyls are indistinguishable from those of heroin with the exception that the fentanyls may be hundreds of times more potent. There are hundreds of fentanyl analogues with each differing only in potency and duration of action. The high potency, thence low dosage required for producing effect, and the multiplicity of active, structural analogues possible make it difficult to detect the fentanyls in the illicit traffic. To date, over 12 different clandestinely produced fentanyl analogues have been identified in the U.S. illicit drug traffic. Over 100 deaths have been attributed to the abuse of these drugs. Although the clandestine synthesis, distribution and abuse of the fentanyls have been confined to the U.S. up to this time, their extremely high potency and relative ease of synthesis make them serious drug abuse threats internationally.

GENERAL HISTORY

Legitimate Use

The parent drug fentanyl was first synthesized by the Janssen Pharmaceutical Company of Belgium in the late 1950's. It was introduced into clinical medicine under the tradename Sublimaze in the 1960's as an intravenous anesthetic and as pre- and post-operative medication. Shortly thereafter, two other fentanyl analogues were developed: alfentanil, an ultra-short (5-10 minutes) acting analgesic, and sufentanil, an exceptionally potent analgesic for use in heart surgery. Today these fentanyls are extensively used for surgical procedures and for the control of pain. Other fentanyl analogues which were developed for legitimate use are carfentanil, a very potent analogue used in capture guns for immobilizing wild animals, and lofentanil, an analogue with a very long duration of action, which may be used in trauma centers for the control of severe pain.

Illicit Use

Illicit use of fentanyl was identified in the mid-1970's when it was reported that pharmaceutical fentanyl was being used as a doping agent in horseracing. There were also reports that the pharmaceutical fentanyls were being diverted and used by physicians, pharmacists and nurses. This continues to be a small, but significant problem in the U.S.

The clandestinely produced fentanyls first appeared in 1979 when alpha-methylfentanyl was finally identified as the cause of a number of unusual overdose deaths in California. Autopsy findings were similar to those found for heroin overdose. It was reported that the victims had used a drug called either "China White" or "synthetic heroin". In retrospect, the victums had been unprepared for the large increase in potency of alpha-methylfentanyl over heroin. Over the next decade, at least 10 different fentanyl analogues appeared on the street and over 100 overdose deaths were linked to the fentanyls. Illicit use of the fentanyls peaked in 1985, then declined gradually. The most recent outbreak of fentanyl deaths occurred in Pittsburgh, Pennsylvania in the fall of 1988. These overdose deaths resulted from the production and distribution of 3-methylfentanyl by a clandestine chemist.

PHARMACOLOGY

General Effects

The pharmacological effects of pharmaceutical fentanyls in humans have been studied in some detail. Unfortunately, there is virtually nothing known about the effects on humans of illicit analogues since they have never been administered to human subjects under controlled conditions. The little we know about the pharmacology of illicit fentanyls comes from studies with laboratory animals. However, these studies suggest all the fentanyls are qualitatively similar in their pharmacological action and the various analogues differ only in their potencies and duration of action.

Fentanyls produce pharmacological effects characteristic of opiates. They produce all the effects of heroin including analgesia, euphoria, pin-point pupils and respiratory depression. Due to their high lipid solubility fentanyls, regardless of route of administration, reach the brain quickly thus providing for a very fast onset of action. The fast onset of action is considered a highly desirable trait by heroin users. Fentanyl users report experiencing the first effects within 90 seconds after intravenous administration and by 2 minutes they are in a relaxed, euphoric state. In non-tolerant individuals, spontaneous breathing can stop at this time, and overdose deaths are likely to occur very rapidly with these drugs.

The duration of the pharmacological effects will vary depending upon the fentanyl analogue used. Opiate-like effects can persist for as little as five minutes, as is the case with alfentanil, or last for one-half hour as is the case for fentanyl. 3-Methylfentanyl has a duration of action of about 4 hours which is similar to that of heroin.

Structure Activity Relationships

With respect to structure-activity relationships, over 200 pharmacologically active fentanyl analogues have been synthesized and studied in experimental animals and various test systems. Many modifications in the basic fentanyl structure (See fentanyl data sheet) result in retention of pharmacological activity. Structural changes generally result only in changes of potency or duration of action, not in intrinsic opiate-like character. For example, potency can be increased by simple substitutions at the alpha and beta positions of the phenethyl side chain; thus, with respect to analgesic potency alpha-methylfentanyl is approximately twice as potent as fentanyl or 200 times as potent as morphine. Greater increases in potency can be achieved by simple substitutions at the 3-position of the piperidine ring, as evidenced by 3-methylfentanyl which is over 6000 times more potent than morphine and is one of the most potent fentanyl analogues. In addition, the benzene ring in the phenethyl side chain can be replaced by thiophene or furan without losing activity. The structure activity relationships for the fentanyls seem to be well understood by the clandestine chemists because at least 10 analogues have been found on the streets. These analogues include 3-methylfentanyl, alpha-methylfentanyl, acetyl-alpha-methylfentanyl, beta-hydroxyfentanyl, thiofentanyl, alpha-methylthiofentanyl, para-fluorofentanyl and beta-hydroxy-3-methylfentanyl.

Routes of Administration and Dosage Forms

The fentanyls are most commonly used by intravenous administration, but like heroin, they may be smoked or "snorted". In fact, some users prefer the intranasal route and there are reports that the drugs are available in two forms: one for "shooters" and one for "snorters". Illicit fentanyls are generally diluted (cut) with very large amounts of lactose or mannitol and occasionally are mixed with cocaine or heroin. Because street samples contain only a small amount of active drug, generally less than 1%, they do not usually have a distinctive colour, odor, or taste. The colour of fentanyl samples may range from pure white (in which case it may be sold as "Persian White"), to an off-white or light tan (sold as "China White", "Synthetic Heroin", or "Fentanyl"), to light or dark brown (sold as "Mexican Brown"). The brown colour is thought to come from lactose which has been heated until it becomes slightly carmalized. Similarly, the texture of the samples may range from light and finely powdered to somewhat coarse, cake-like and crumbly, resembling powdered milk. Occasionally, fentanyl samples may have a medicinal or chemical odor, but this is not characteristic. There is nothing about the appearance of fentanyl samples that is unique, and it is impossible to distinguish them from heroin except by chemical analysis.

Pharmacokinetics

Current information on the pharmacokinetics of fentanyls has been derived from studies using pharmaceutical fentanyls. Although there is general agreement on the basic way in which the pharmaceutical fentanyls are distributed, metabolized and eliminated, there is considerable disagreement on the quantitative description of these processes. Quite different pharmacokinetic values have been reported by various investigators and whether these differences are due to an intrinsically large biological variability of these drugs or to differences in analytical methods has not been determined. Unfortunately, there is very little known about the pharmacokinetics of the illicit analogues since they have been tested to a very limited extent in laboratory animals.

The fentanyls are usually administered intravenously or intramuscularly, thus there is no clinical data available on their gastrointestinal, intranasal or pulmonary absorption. Fentanyls are very lipid soluble and therefore should move easily and rapidly across any membrane barrier and should be efficiently absorbed by any route of administration. Following intravenous administration, the fentanyls rapidly disappear from the bloodstream and are extensively distributed throughout the body where they are bound to peripheral tissues, plasma proteins and red blood cells. Within 5 minutes of administration, over 90% of a dose of fentanyl will be eliminated from the plasma via sequestration in peripheral tissues. Because of this rapid redistribution, the resulting fentanyl concentrations in blood and other body fluids are extremely low and thus very difficult to detect.

Fentanyls are cleared from the body via metabolism followed by urinary excretion of metabolites. The fentanyls are rapidly and extensively metabolized, generally to more polar metabolites that are pharmacologically inactive. The major metabolic route is oxidative N-dealkylation to normetabolites. Amide hydrolysis to the despropionyl metabolite occurs to a lesser extent and hydroxylation of the piperidine ring, the phenyl rings, or the propionyl sidechain occurs to a minor extent. The fentanyls are eliminated as their more polar metabolites primarily in urine. Clinical studies have shown that nearly one-half of an administered dose of fentanyl is excreted within the first 8 hours and about 70% of the total dose will be eliminated by 72 hours. Less than 10% of an administered dose will be eliminated as unchanged parent drug. This also adds to the difficulty in detecting fentanyl use.

An exceptionally wide range of pharmacokinetic values has been reported for the fentanyls. There is general agreement that the half-life of the initial phase (which describes the distribution of drug from plasma to the tissues) is short, approximately 15 minutes; however, there is little consensus on the values for the later elimination phase(s). This disagreement may be related to the difficulty of accurately measuring the very low concentrations of drug (generally 10 ng/ml or less) present in blood and urine. Consequently, those investigators who report detection limits for fentanyl at subnanogram levels, also report longer terminal half-lives and slower clearance rates. However, the large discrepancies in values reported by many investigators seem too great to be attributed to differences in analytical precision or accuracy. For example, reported half-life values for fentanyl range from 2.4 to 14.2 hours, while values for volume of distribution range from 150 to 381 L and clearance values range from 150 to 991 mg/min. It is possible that these differences reflect true biological variability rather than differences in analytical techniques. Fentanyl elimination may be influenced by dose and age.

TOXICOLOGY

Toxic Clinical Manifestations of Drug Use and Overdose

Fentanyls produce all the effects and side effects of the classical narcotic analgesics. They are among the most potent respiratory depressants and analgesics discovered to date and can produce profound pain relief at remarkably low doses. Other effects include euphoria, pin-point pupils, nausea and an increase in muscle tone commonly called "Wooden Chest" or "lead-pipe rigidity". A transient drop in heart rate and blood pressure, effects not usually found with heroin use, are observed in surgical patients receiving fentanyls. Respiratory depression and coma are the most serious adverse effects of the fentanyls. Fentanyl plasma levels above 2-3 ng/ml are associated with respiratory depression which may be life threatening.

Chronic use of fentanyls does not typically produce any damage to organs or tissues. Bacterial and viral infections may develop from the use of infected needles. When used regularly, the fentanyls produce narcotic-like tolerance and physiological dependence. Experienced heroin users report that the effects of the fentanyls are similar to, and are an acceptable substitute for, heroin. Fentanyls thus appear to have an abuse liability equivalent to heroin.

Forensic Toxicology

In the U.S. over 100 overdose deaths have been linked to the use of the illicit fentanyl analogues with perhaps 1/10 that number associated with the abuse of the pharmaceutical fentanyls. The latter cases involved health professionals who were apparently able to divert pharmaceutical drugs for their own use.

Demographic studies of fentanyl-related deaths in California suggest that the typical fentanyl overdose victim is similar to the typical heroin user in nearly all respects. This person is likely to be male (78% compared with 22% female), 32 years of age (range, 19-57 years), and Caucasian (50% compared with 29% Hispanic, 20% Afro-American, and 0.9% Asian). A large portion of the fentanyl-related deaths occurred in suburban and rural areas of California, not in large metropolitan areas.

Autopsy Findings

Pulmonary edema and congestion are found in nearly all cases of fentanyl overdose deaths. Old needle puncture scars and new injection sites are also common findings. Autopsy findings and circumstances surrounding fentanyl deaths are similar to the "sudden deaths" reported for heroin. Those autopsy findings generally associated with death from respiratory depression, such as broncho-pneumonia, or aspiration of gastric contents into the lungs, are rarely found in fentanyl deaths. In addition, there is no evidence of anaphylaxis or allergic reaction from contaminants in the syringe. The most likely cause of death is simply a very rapid cessation of respiration which is quite consistent with the known pharmacological properties of the fentanyls. These highly lipophyllic drugs can reach the brain very rapidly after intravenous administration. It has been observed that maximum respiratory depression occurs within 2-5 minutes in surgical patients receiving fentanyl. Interestingly, although most of the fentanyl victims had a long history of intravenous drug use, there was very little pathology observed at autopsy. Even chronic liver inflammation or cirrhosis was rare. The use of ethyl alcohol is thought to be a significant risk factor in increasing the probability of overdose. Ethanol was found in a surprisingly large number of overdose cases and was often present at intoxicating levels.

Blood and Tissue Levels

Alpha-methylfentanyl and 3-methylfentanyl are the analogues that have been most commonly associated with fentanyl analogue overdoses. Since 1985, overdoses have involved 3-methylfentanyl almost exclusively. The concentrations of the fentanyls in the body fluids and tissues are extraordinarily low, generally in the low nanogram range. The mean fentanyl concentration found in the blood of overdose victims, as measured by a radioimmunoassay highly specific for the fentanyls, was approximately 3.0 ng/ml, but ranged from 0.2 to greater than 50 ng/ml. The mean urine concentration of drug found was approximately 4.0 ng/ml with a range of 0.2 to greater than 800 ng/ml. Similar drug concentrations in body fluids have been reported in overdose cases in which the individuals administered pharmaceutical fentanyl. Curiously, very few other drugs were found during toxicological analysis. Although most of the fentanyl victims were known heroin users, morphine or codeine was rarely found.

In summary, fentanyl overdose cases may seem a paradox at the post mortem examination. Autopsy findings of pulmonary edema and needle marks clearly point to a narcotic overdose; however, using routine toxicological methods no drug, or only trace levels of drug, will be detected. Only through the use of analytical procedures specific for the fentanyls will the laboratory be able to detect the fentanyls.

CLINICAL MANAGEMENT

Respiratory depression is the most serious toxic effect of the fentanyls. This can be quickly and effectively reversed by naloxone (Narcan). Naloxone is a specific opiate antagonist and is the antidote of choice; however, because the fentanyls are so extraordinarily potent, higher doses than are normally used may be required (e.g., milligrams rather than micrograms). Naloxone must be administered quickly, because life-threatening respiratory depression occurs within minutes after administration of the fentanyls. Repeated naloxone administration may be necessary when dealing with a long acting fentanyl analogue.

CLANDESTINE SYNTHESIS

Synthesis I

Fentanyl and many of its analogues can be synthesized through either norfentanyl or 3-methyl-norfentanyl intermediates which are prepared from the appropriate 1-benzyl-4-piperidone. The appropriate piperidone is reductively aminated with aniline, acylated with an anhydride and hydrogenated to form the norbase. Fentanyl and the specific analogues are then prepared by alkylation of the piperidine nitrogen. Variation of the aniline, acyl and alkylating groups allows the preparation of a wide vaiety of fentanyl analogues.

Synthesis II

Fentanyl and some analogues may be prepared directly by the condensation of commercially available 1-(beta-phenethyl)-4-piperidone with aniline followed by reduction and acylation.

Synthesis III

Alternative syntheses involve the preparation of appropriate 4-piperidones through addition of an alkylamine resulting in acrylate or methacrylate esters followed by ring closure through a Dieckman condensation and subsequent hydrolysis and decarboxylation. Reductive amination with aniline followed by acylation with an anhydride yields fentanyl or the desired analogue.

Precursors and Essential Chemicals

1-Benzyl-4-piperidone or 1-benzyl-3-methyl-4-piperidone (I)
1-(beta-phenethyl)-4-piperidone (II)
Methyl acrylate or methyl methacrylate (III)
Alkylamine such as phenethylamine or amfetamine or phenylethanolamine (III)
Aniline or p-fluoroaniline (I,II,III)
Propionic anhydride or acetic anhydride (I,II,III)
2-Phenyl-1-bromoethane or 2-phenyl-1-bromopropane or 2-(2-thienyl)-ethanol tosylate or 1-(2-thienyl)-2-propanone or styrene oxide (I,II)
Sodium cyanoborohydride, sodium borohydride or lithium aluminum hydride (I,II,III)
Sodium methoxide (III)
p-Toluenesulfonic acid (I,II,III)

ANALYTICAL CHEMISTRY

Body Fluids

Generally speaking, fentanyls are difficult to detect in biological fluids. They do not react with commercially available screening reagents for the opiates. Because they are normally present in such small amounts in body fluids, very sensitive assayss are required to detect and quantitate fentanyl and its metabolites and analogues. A review of analytical methods utilized for the determination of fentanyl and its metabolites and analogues has recently been written by Watts and Caplan (1989).

Extraction

A number of extraction procedures for fentanyl and its metabolites and analogues have been described in the literature (Gillespie et al. 1981; Van Rooy et al. 1981; Goromaru et al., 1984; Hammargren and Henderson, 1988). Use of teflon-lined caps on extraction tubes and silanization of all extraction glassware allows for higher recovery of fentanyl.

Immunoassay

Radioimmunoassay techniques have been developed for the detection of fentanyl and its analogues (Henderson et al., 1975; Michiels et al., 1977; Phipps et al., 1983; Schuttler and White, 1984). Antisera have been produced which are specific for the 4-monosubstituted piperidine analogues such as fentanyl and all the known illicit analogues. Other antisera have been developed which are specific for the 4,4-disubstituted piperidine analogues which include sufentanil and alfentanil. The respective antisera are highly specific and there is litle cross reactivity between the two basic types of fentanyl analogues. In addition, neither of the antisera cross react with common drugs of abuse or with most of the known metabolites. Radioimmunoassays using these antisera are quite sensitive and have detection limits in biological fluids in the picogram per milliliter range. Also, a solid-phase fentanyl immunoassay has been developed which can be used to rapidly screen powder and paraphernalia samples for the illicit fentanyls (Henderson et al., 1990).

Chromatography

Gas Chromatography

Fentanyl and its metabolites have been measured in human plasma, whole blood and/or urine using gas chromatography coupled to either a flame ionization detector (GC-FID) or a nitrogen phosphorus detector (GC-NPD) (Gillespie et al., 1981; Van Rooy et al., 1981; Phipps et al., 1983; Bjorkman and Stanski, 1988; Watts and Caplan, 1988; Kintz et al., 1989). The more sensitive GC-NPD technique detects fentanyl concentrations in the picogram/ml range. The GC-FID has a higher fentanyl detection limit of around 3 nanograms/ml of plasma. Using GC-NPD and GC-FID, the fentanyl metabolites, 1-(2-phenethyl)-4-N-anilinopiperidine and 4-N-(N-propionylanilino)piperidine, have been detected in picogram amounts in human plasma (Van Rooy, 1981; Kintz et al., 1989). Hammargren and Henderson (1988), using capillary column gas chromatography with an electron capture detector (GC-ECD), measured norfentanyl levels in urine. Following differential pH extraction, norfentanyl was derivatized with pentafluoroproprionic anhydride prior to measurement with the GC-ECD. The detection limit for this assay was 2 nanograms/ml of urine sample.

Gas chromatography has also been used to measure selected fentanyl analogues. GC-NPD has been used to measure plasma levels of alfentanil, sufentanil and lofentanil in plasma. This same techinque was used by Gillespie et al. (1982) to quantitate alpha-methylfentanyl levels in human blood, bile and liver tissue. Hammargren and Henderson (1988) recently reported the use of capillary column GC-ECD for the determination of nor-3-methylfentanyl in human urine. This compound is the N-dealkylated metabolite of 3-methylfentanyl. Nor-3-methylfentanyl was extracted from urine using a differential pH extraction technique and subsequently derivatized with pentafluoroproprionic anhydride. The limit of sensitivity of this technique was 2 nanograms/ml of urine.

High Performance Liquid Chromatography (HPLC)

Kumar et al. (1987) developed an HPLC technique for measuring levels of fentanyl and alfentanyl in plasma. Detection was accomplished using an ultraviolet detector. The detection limit for the assay was 1.0 ng/ml for both fentanyl and alfentanil, thus making its sensitivity somewhat comparable to gas chromatographic techniques.

Spectrometry

Mass spectrometry techniques may be used as confirmatory tests for fentanyl and its metabolites and analogues. Gas chromatography/mass spectrometry (GC/MS) has been used to measure fentanyl in human plasma and whole blood (Van Rooy et al., 1981; Lin et al., 1981; Watts and Caplan, 1988). Detection limits ranged from 0.05 to 0.25 nanogram/ml of sample. The GC/MS was used by Goromaru et al. (1984) to quantitate human urine levels of fentanyl and three of its metabolites 4-N-(N-propionylanilino)piperidine, 4-N-(N-hydroxypropionylanilino)piperidine and 1-(2-phenethyl)-4-N-(N-hydroxypropionylanilino)piperidine. Fentanyl and metabolites were isolated from urine using a differental pH extraction technique and subsequently derivatized with trimethylsilylacetamide. Identification and quantitation of the TMS derivatives of fentanyl and its metabolites were made using selected ion monitoring (SIM).

Solid Dosage Forms

Melting Point Determinations

Melting points of fentanyl, a-methylfentanyl, 3-methylfentanyl and para-flurofentanyl were obtained from Gunn. Melting points of a-methylthiofentanyl, ß-hydroxyfentanyl, ß-hydroxy-3-methylfentanyl, thiofentanyl and (±)-cis-3-methylthiofentanyl were obtained from NIDA (1988).

Colour Tests

Fentanyl and a-methylfentanyl were examined using the Marquis colour reaction test (Allen et al., 1981; Moffat, 1986).

Chromatography

Thin-Layer Chromatography.

The following thin layer chromatography systems were used.

System A: Hexane : isopropyl alcohol : diethylamine (30:3:0.5), Silica gel (Whatman K6). Visualization using iodine vapors. (Allen et al., 1981)

System B: Methanol : strong ammonia solution (100:1.5), silica gel G/0.1M potassium hydroxide. Visualization with acidified iodoplatinate. (Moffat, 1986)

System C: Cyclohexane : toluene : diethylamine (75:15:19), silica gel G/0.1M potassium hydroxide. Visualization with acidified iodoplatinate. (Moffat, 1986)

System D: Chloroform : methanol (90:10), silica gel G/0.1M potassium hydroxide. Visualization with acidified iodoplatinate. (Moffat, 1986)

System E: Acetone : chloroform (1:2), silical gel F. Detection with UV light (254 nm) and 1% iodine in methanol or Dragendorff reagent or iodoplatinate. (Suzuki et al.,1986)

System F: Benzene : chloroform : methanol (2:10:1), silical gel F. Detection with UV light (254 nm) and 1% iodine in methanol or Dragendorff reagent or iodoplatinate. (Suzuki et al., 1986)

System G: Chloroform : hexane : methanol (10:2:1), silical gel F. Detection with UV light (254 nm) and 1% iodine in methanol or Dragendorff reagent or iodoplatinate. (Suzuki et al., 1986)

System H: Chloroform : methanol : concentrated ammonium hydroxide (90:10:4 drops per 100 ml), silica gel (E. Merck analytical plates). Visualization with iodine. (NIDA, 1988)

System I: Chloroform : methanol : concentrated ammonium hydroxide (96:4:4 drops per 100 ml) silica gel (E. Merck analytical plates). Visualization with iodine. (NIDA, 1988)

System J: Methylene chloride : methanol : concentrated ammonium hydroxide (85:15:1), silica gel (E. Merck analytical plates). Visualization with iodine. (NIDA, 1988)

System K: Methylene chloride : methanol (9:1), silica gel (E. Merck analytical plates). Visualization with iodine. (NIDA, 1988)

System L: Chloroform : methanol (9:1), silica gel (E. Merck analytical plates). Visualization with iodine. (NIDA, 1988)

Additional References: Heagy (1986)

Gas Chromatography

Gas chromatographic (GC) data were obtained from Cooper et al., (1986). Data are expressed as the relative retention time (RRT) of the substance relative to fentanyl (fentanyl retention time (RT) = 16.68 minutes). The following parameters were used.

Column. 12 m by 0.20 mm inside diameter fused-silica capillary column coated with SE-54 (Hewlett-Packard, Avondale, PA, USA) at a film thickness of 0.24 um.
Column Temp. Programmed as follows: initial temperature, 210# C; initial hold, 2 min; temperature programme rate, 2# C/min; final temperature, 280# C; and final hold, none.
Injection Temp. 300# C.
Carrier Gas. Hydrogen at a flow rate of 50 cm/s.
Internal Standard. n-Triacontane.
Detector. Flame ionization detector.
Detector Temp. 300# C.

Additional References: Allen et al., 1981; Allen and Lurie, 1984; Moffat, 1986; Cooper et al., 1981; Gunn; Mills and Roberson, 1987; Moore et al., 1986; Suzuki et al., 1986; Watts and Caplan, 1988.

High Performance Liquid Chromatography

High performance liquid chromatography (HPLC) data were obtained from Lurie et al. (1984). Data are expressed in terms of the relative retention time (RRT) and corrected 215/230 absorbance ratio (RAR) of the compound relative to those of fentanyl. Corrected absorbance ratios obtained by peak height for the individual analogues were determined by dividing the absorbance ratio for a compound by the absorbance ratio of the internal standard, fentanyl. The following parameters were used.

> Column. Prepacked 4.6mm x 25cm stainless steel column, with 10 um C18 packing material (Partisil 10-ODS-3, Whatman).
> Mobile Phase. 81% phosphate buffer (99 parts water, 3 parts 2N sodium hydroxide and 1 part phosphoric acid), 4% methanol, 10% acetonitrile and 5% tetrahydrofuran.
> Internal Standard. Fentanyl
> Detector. Variable UV detector set at 215 nm or 254 nm containing a 2.5 ul flow cell, either alone or in series with a second variable UV detector set at 230 nm and containing a 1.5 ul flow cell (Perkin-Elmer).

Additional References: Allen and Lurie, 1984; Cooper et al., 1981; Gunn; Kumar et al., 1987; Mills and Roberson, 1987; Wilson et al., 1988.

Spectroscopy/Spectrometry

Intrared Spectroscopy.

Infrared (IR) spectra of the hydrochlorides of fentanyl and its analogues were obtained from Cooper et al. (1986). Infrared spectra were recorded in potassium bromide with a Beckman model 4240 spectrophotometer.

Additional References: Allen et al., 1981; Allen and Lurie, 1984; Moffat, 1986; Cooper et al., 1981; Gunn; Heagy, 1981; Mills and Roberson, 1987; Suzuki, 1989; Suzuki et al., 1986.

Ultraviolet Spectroscopy.

Ultra-violet (UV) spectral data were obtained from Mills and Roberson (1987). Spectra were obtained using a Hewlett-Packard 8450A or 8451A diode array spectrophotometer. Transmittance was determined over a wavelength range from 220 to 340 nm. Data is expressed as the wavelengths showing maximum absorbance in acidic and basic solutions.

Mass Spectrometry

Mass spectral data on fentanyl and its analogues were obtained from the U.S. Drug Enforcement Administration Special Testing and Research Laboratory. The mass spectrometers employed utilized quadrupole mass analyzers (Finnigan 4000 and 4600) and were operated under electron ionization conditions at 70 eV.

Additional References: Allen et al., 1981; Allen and Lurie, 1984; Cheng et al., 1982; Moffat, 1986; Cooper et al., 1981; Cooper et al., 1986; Gunn; Mills and Roberson, 1987; Suzuki et al., 1986.

FENTANYL

CAS Registry Number: 437-38-7; 990-73-8 (Citrate)

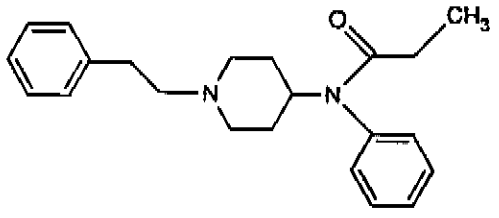
IUPAC Name: N-(1-Phenethyl-4-piperidyl)propionanilide

CA Index Names: N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide
N-(1-Phenethyl-4-piperidyl)propionanilide

Other Names: N-(1-Phenethyl-4-piperidinyl)-N-phenylpropanamide
N-(1-Phenethyl)-4-(N-propananilido)piperidine
1-(2-Phenylethyl)-4-(N-propananilido)piperidine
R 4263

International Control: I, 1961 Convention

Chemical Structure:



M.F.: $C_{22}H_{28}N_2O$ **M.W.:** 336.46
$C_{22}H_{28}N_2O.C_6H_8O_7$ (Citrate) 528.60 (Citrate)

Physical Appearance: Fentanyl base exists as crystals. Fentanyl citrate is a crystalline powder.

Chemical/Physical Properties:

M.P.: 83-84 °C (Base); 149-151 °C (Citrate)

Solubility: Fentanyl citrate is soluble 1 in 40 of water, 1 in 140 of ethanol, 1 in 350 of chloroform and 1 in 10 of methanol; slightly soluble in ether.

Stereochemistry: No stereoisomers

Colour Tests. Marquis - orange.

Thin-Layer Chromatography. System B - Rf 0.70 (Ref: Codeine = 0.06); System C - Rf 0.45 (Ref: Pethidine = 0.37); System D - Rf 0.74 (Ref: Caffein = 0.58).

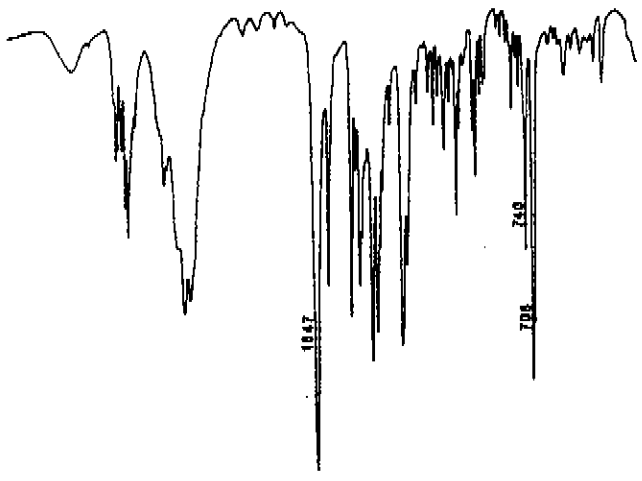
Gas Chromatography. RT-16.68 minutes. RRT-1.00

High Performance Liquid Chromatography. RRT-1.00, RAR-1.00

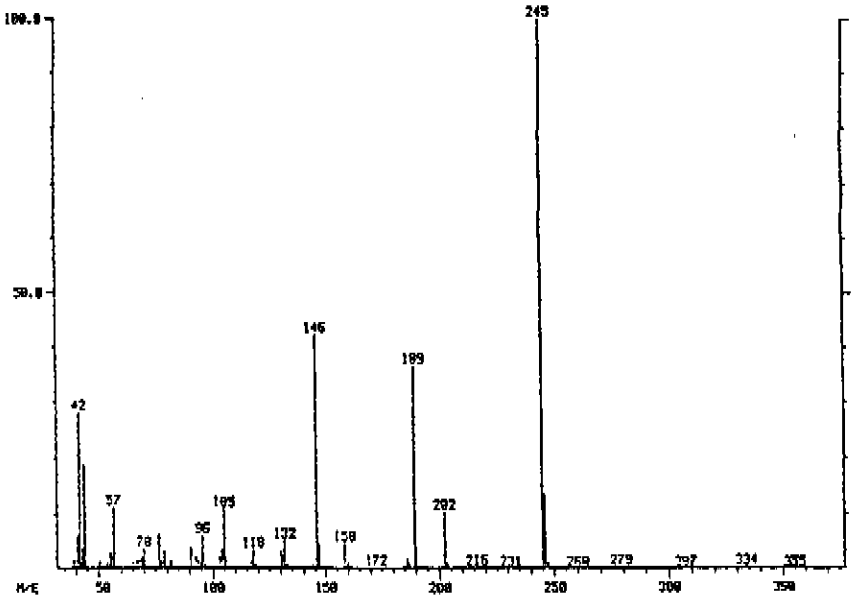
Ultraviolet Spectroscopy.

Acidic Solutions - 251 nm, 256 nm, 262 nm

Infrared Spectrum.
HCl



Mass Spectrum.



ALPHA-METHYLFENTANYL

CAS Registry Numbers: 79704-88-4; 53757-42-9 (Racemate)

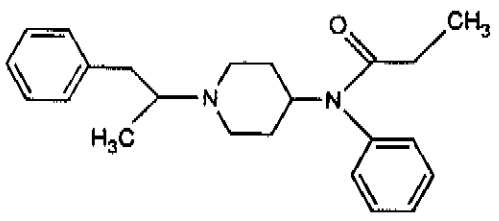
IUPAC Name: N-[1-(2-Phenylisopropyl)-4-piperidyl]propionanilide

CA Index Name: N-[1-(2-Phenylisopropyl)-4-piperidinyl]-N-phenylpropanamide

Other Names: N-[1-(Alpha-methylphenethyl)-4-piperidyl]propionanilide
1-(1-Methyl-2-phenylethyl)-4-(N-propananilido)piperidine
R 4481; NIH 9961; UM 1324; MCV 4287; China White; Methylfentanyl; Synthetic Heroin

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{23}H_{30}N_2O$ **M.W.:** 350.46
$C_{23}H_{31}ClN_2O$ (HCl) 386.96 (HCl)

Chemical/Physical Properties.

M.P.: 266-270 °C w/decomposition (HCl)

Stereochemistry: 2 Enantiomers and 1 racemate

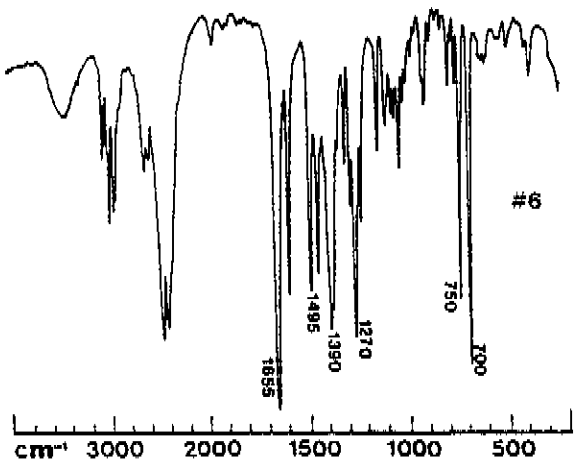
Colour Tests. Marquis - weak orange

Thin Layer Chromatography. System A - Rf 0.60; System E - Rf 0.25; System F - Rf 0.62; System G - Rf 0.60.

Gas Chromatography. RRT-1.082

High Performace Liquid Chromatography. RRT-1.22, RAR-1.08

Infrared Spectrum.
HCl



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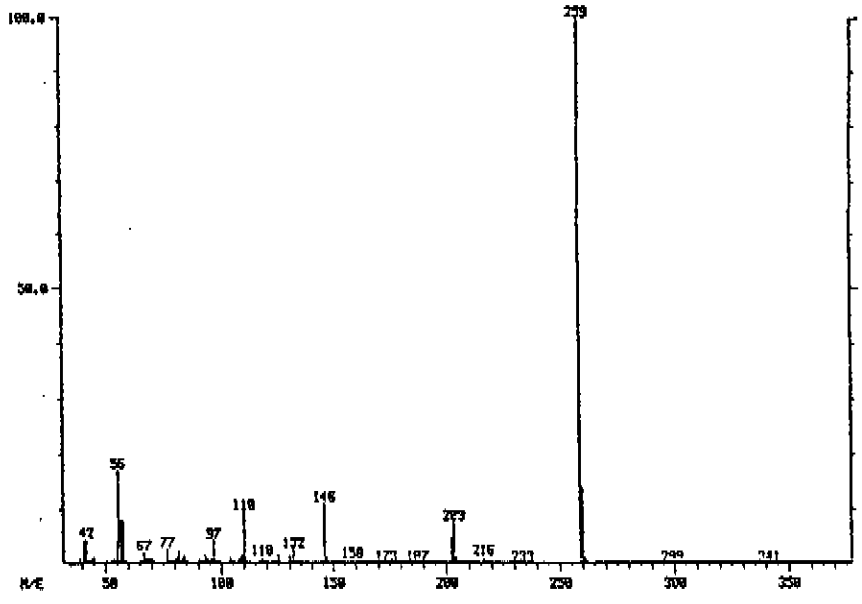
Mass Spectrum.



ACETYL-ALPHA-METHYLFENTANYL

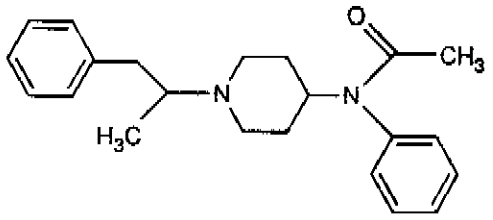
CAS Registry Number: 101860-00-8

IUPAC Name: N-[1-(1-Methyl-2-phenylethyl)-4-piperidinyl]-N-phenylacetamide

CA Index Name: N-[1-(a-Methylphenethyl)-4-piperidyl]acetanilide

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{22}H_{28}N_2O$ **M.W.:** 336

Chemical/Physical Properties.

Stereochemistry: 2 Enantionmers and 1 racemate.

Gas Chromatography. RRT-1.003

ALPHA-METHYLTHIOFENTANYL

CAS Registry Number: 103963-66-2

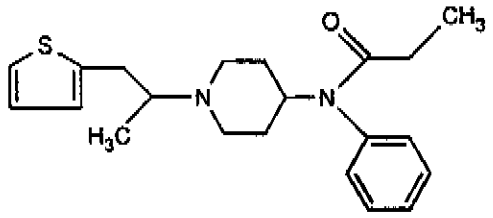
IUPAC Name: N-[1-[Methyl-2-(2-thienyl)ethyl]-4-piperidyl]propionanilide

CA Index Name: N-[1-[Methyl-2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide

Other Names: N-[1-(1-Methyl-2-(2-thienyl)ethyl)-4-piperidyl]-N-phenylpropanamide
a-Methylthiofentanyl; NIH 10538; MCV 4583

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{21}H_{28}N_2OS$ **M.W.:** 356.53
$C_{21}H_{29}N_2ClOS$ (HCl) 392.99 (HCl)

Physical Appearance: The hydrochloride is a white solid powder.

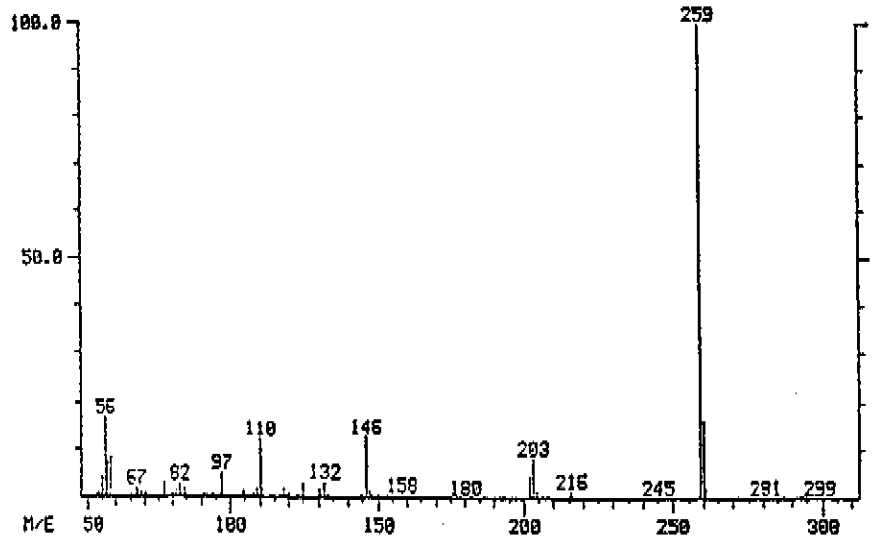
Chemical/Physical Properties.

M.P.: 243-245 °C (HCl)

Stereochemistry: 2 Enantiomers and 1 racemate.

Thin-Layer Chromatography. System H - Rf 0.87.

Mass Spectrum.



3-METHYLFENTANYL

CAS Registry Number: 42045-86-3; individual isomers have CAS numbers as follows: 78995-19-4; 53758-16-0; 78995-17-2; 53758-18-2; 53758-22-8; 53758-20-6; 65814-07-5

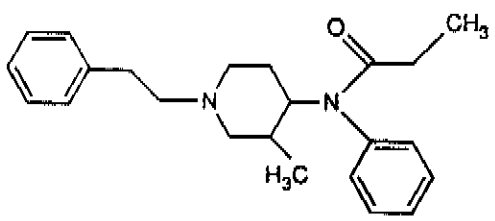
IUPAC Name: N-(3-Methyl-1-phenethyl-4-piperidyl)propionanilide

CA Index Name: N-[3-Methyl-1-(2-phenylethyl)-4-piperidinyl]-N-phenylpropanamide

Other Names: Mefentanyl; F 7209. NIH 10456 and MCV 4522 are specific names for racemic cis-3-methylfentanyl. NIH 10457 and MCV 4523 are specific names for racemic trans-3-methylfentanyl.

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{23}H_{30}N_2O$ **M.W.:** 350.51

Chemical/Physical Properties.

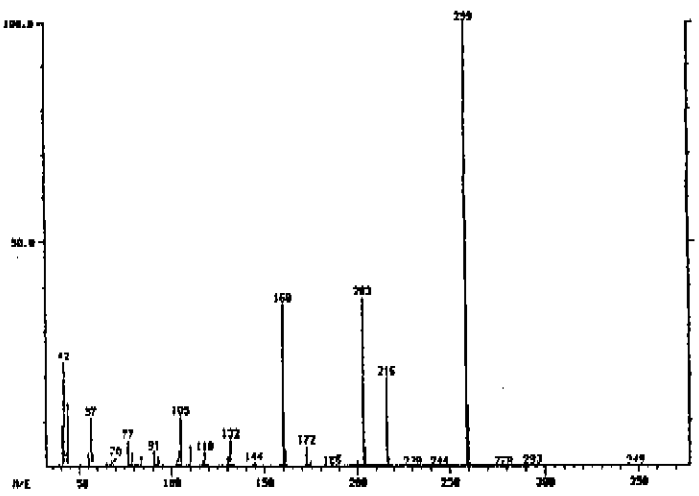
M.P.: 151-161 °C (Base)

Stereochemistry: 2 Sets of diastereomers each of which contains an enantiomeric pair.

Thin-Layer Chromatography. System E - Rf 0.35; System F - Rf 0.69; System G - Rf 0.68

Gas Chromatography. RRT-1.065

Mass Spectrum.



PARA-FLUOROFENTANYL

CAS Registry Number: 90736-23-5

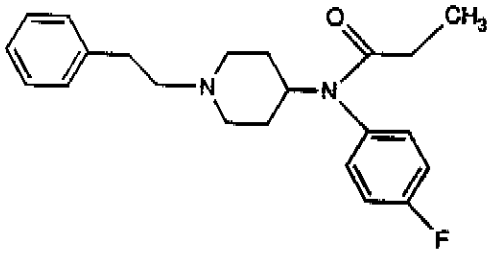
IUPAC Name: 4'-Fluoro-N-(1-phenethyl-4-piperidyl)propionanilide

CA Index Name: N-(4-Fluorophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide

Other Names: Para-fluorofentanyl; p-Fluorofentanyl; NIH 10022; MCV 4323; NIH 10491

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{22}H_{27}FN_2O$ M.W.: 354.47
$C_{22}H_{28}FClN_2O$ (HCL) 390.93 (HCl)

Physical Appearance: Para-Fluorofentanyl hydrochloride is a white solid.

Chemical/Physical Properties.

M.P.: 248-251 °C w/decomposition (HCl)

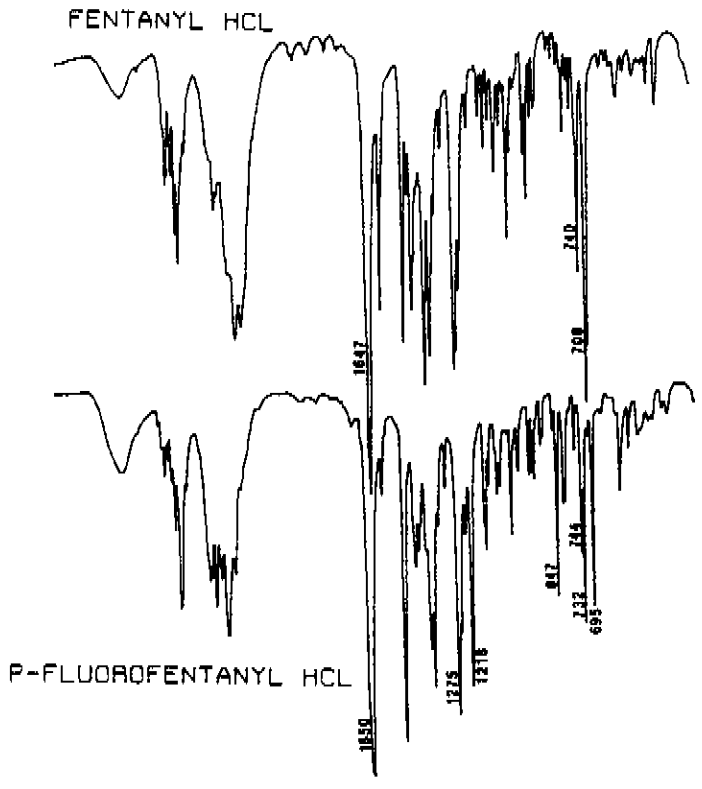
Stereochemistry: No stereoisomers.

Thin-Layer Chromatography. System I - Rf 0.69

Gas Chromatography. RRT-0.951

High Performance Liquid Chromatography. RRT-1.24, RAR-1.42

Infrared Spectrum.



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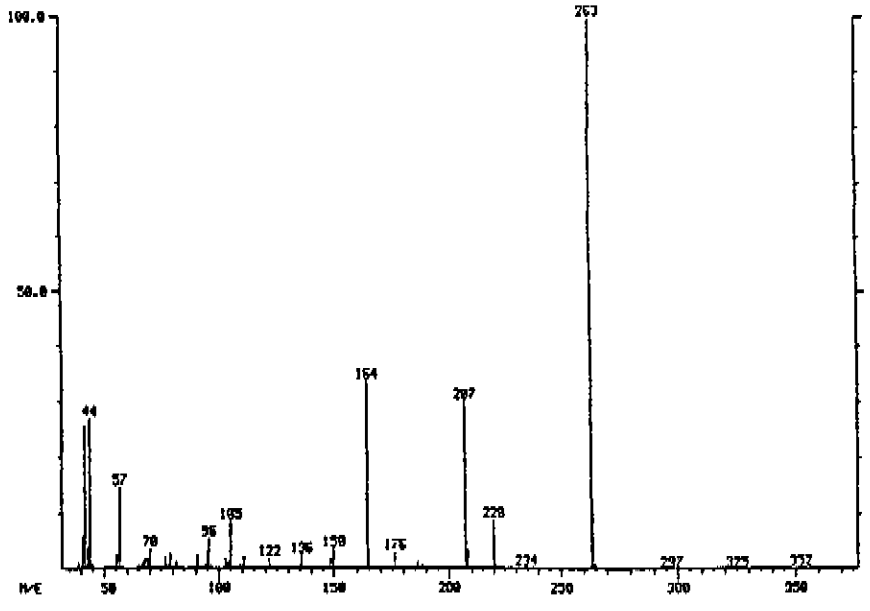
Mass Spectrum.



BETA-HYDROXYFENTANYL

CAS Registry Number: 78995-10-5

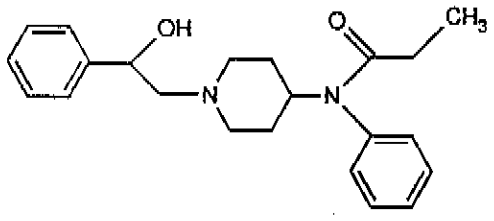
IUPAC Name: N-[1-(ß-Hydroxyphenethyl)-4-piperidyl]propionanilide

CA Index Name: N-[1-(2-Hydroxy-2-phenylethyl)-4-piperidinyl]-N-phenylpropanamide

Other Names: ß-Hydroxyfentanyl; NIH 10506; MCV 4568

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{22}H_{28}N_2O_2$ **M.W.:** 352.48
$C_{22}H_{29}ClN_2O_2$ (HCl) 388.94 (HCl)

Physical Appearance: ß-Hydroxyfentanyl hydrochloride is a white solid.

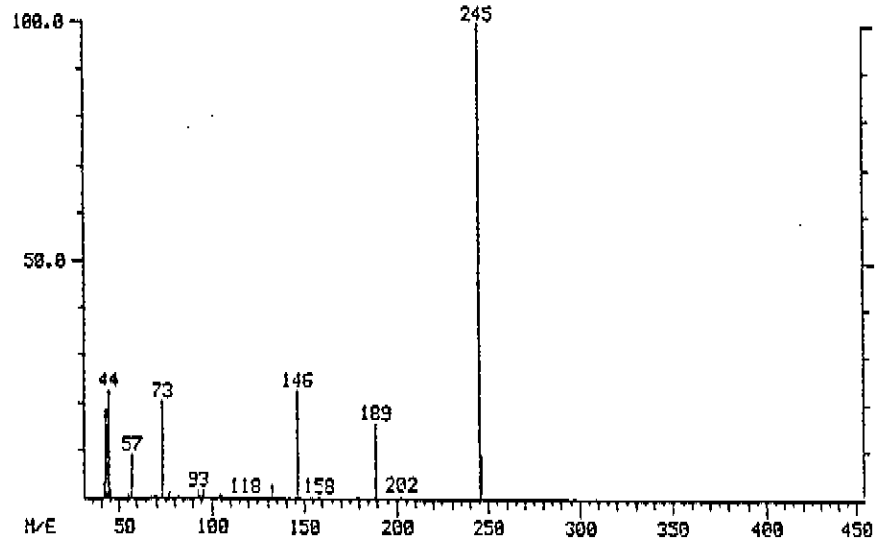
Chemical/Physical Properties.

M.P.: 226-228 °C (HCl)

Stereochemistry: 2 Enantiomers and one racemate.

Thin-Layer Chromatography. System J - Rf 0.84.

Mass Spectrum.
Trimethylsilyl derivative



BETA-HYDROXY-3-METHYLFENTANYL

CAS Registry Number: 78995-14-9

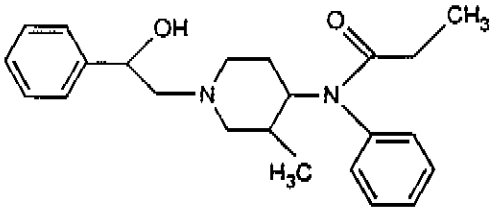
IUPAC Name: N-[1-(ß-Hydroxyphenethyl)-3-methyl-4-piperidyl]propionanilide

CA Index Name: N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidinyl]-N-phenylpropanamide

Other Names: ß-Hydroxy-3-methylfentanyl; Ohmefentanyl; F 7302; NIH 10551; OMF

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{23}H_{30}N_2O_2$ — **M.W.:** 366.51
$C_{23}H_{31}ClN_2O_2$ (HCl) 392.97 (HCl)

Physical Appearance: (+)-Cis-ß-Hydroxy-3-methylfentanyl hydrochloride.1/4 H_2O is a white solid.

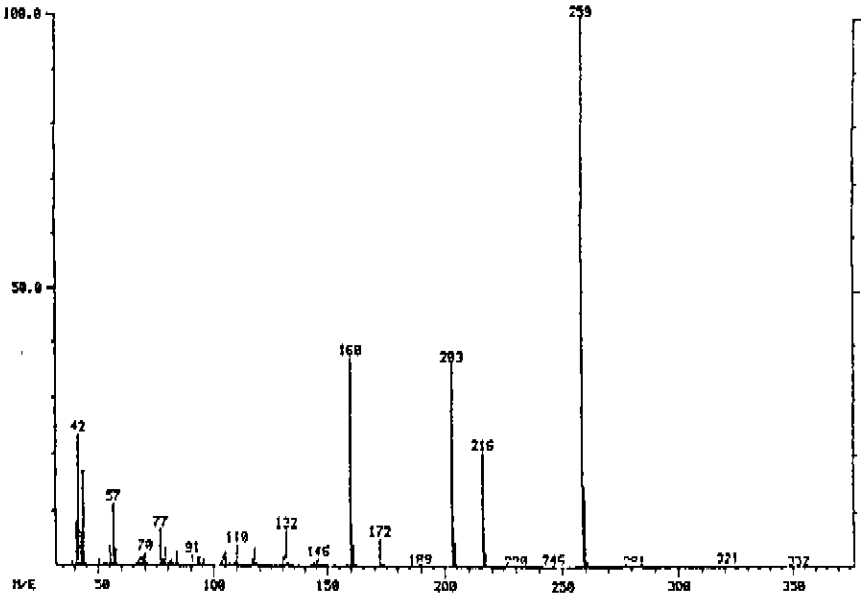
Chemical/Physical Properties.

M.P.: 178-180 °C (HCl)

Stereochemistry: 4 sets of diastereomers each of which contains an enantiomeric pair.

Thin-Layer Chromatography. System K - Rf 0.72.

Mass Spectrum.



THIOFENTANYL

CAS Registry Number: 1165-22-6

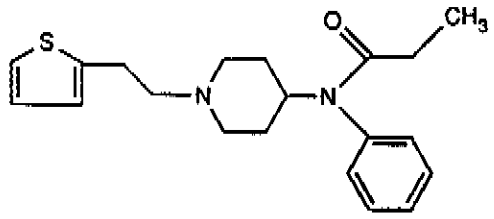
IUPAC Name: N-[1-[2-(Thienyl)ethyl]-4-piperidyl]propionanilide

CA Index Name: N-Phenyl-N-[1-[2-(2-thienyl)ethyl]-4-piperidinyl]propanamide

Other Names: Thiofentanyl; NIH 10505; MCV 4567

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{20}H_{26}N_2OS$ M.W.: 342.51
$C_{20}H_{27}ClN_2OS$ (HCl) 379.00 (HCl)

Physical Appearance: Thiofentanyl hydrochloride is a white powder.

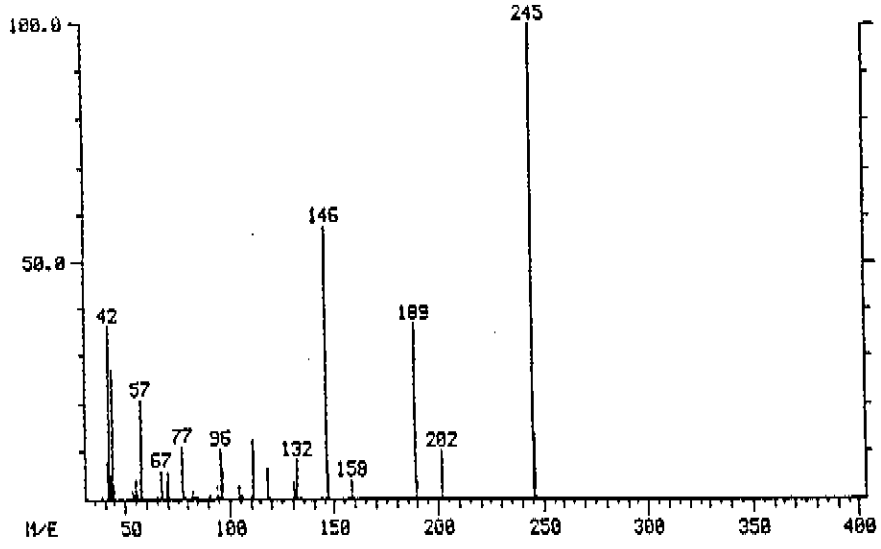
Chemical/Physical Properties.

M.P.: 62-63 °C (Base); 249-251 C (HCl)

Stereochemistry: No stereoisomers.

Thin-Layer Chromatography. System L - Rf 0.69.

Mass Spectrum.



3-METHYLTHIOFENTANYL

CAS Registry Number: 86052-04-2

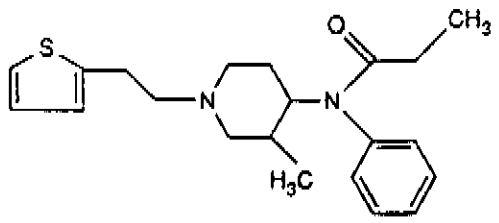
IUPAC Name: N-[3-Methyl-1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide

CA Index Name: N-[3-Methyl-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide

Other Names: 3-Methylthiofentanyl; NIH 10546; MCV 4591

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{21}H_{28}N_2OS$ **M.W.:** 356.53
$C_{21}H_{29}ClN_2OS$ (HCl) 393.00 (HCl)

Physical Appearance: (+)-Cis-3-Methylthiofentanyl hydrochloride.1/2 H_2O is a white solid.

Chemical/Physical Properties.

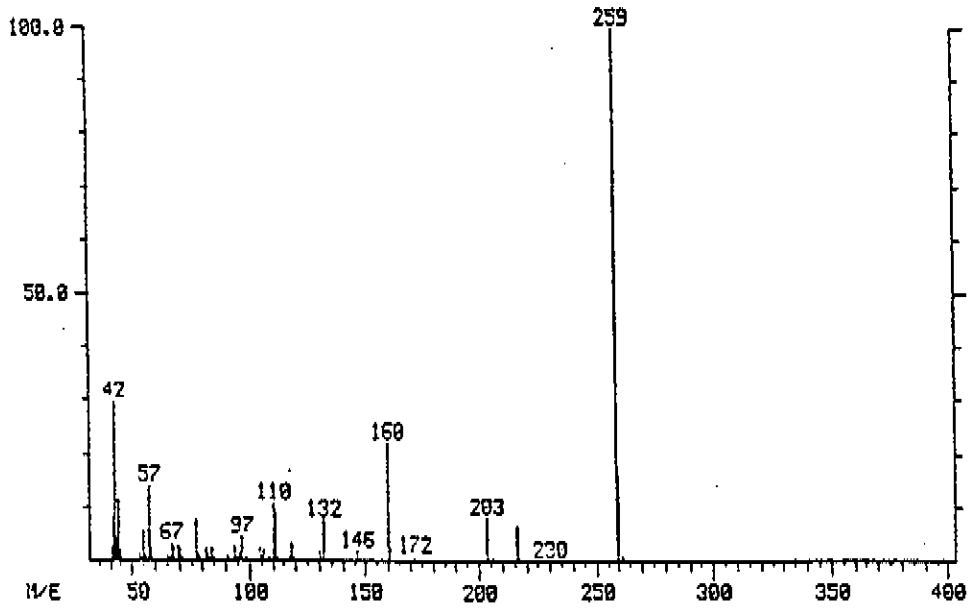
M.P.: 181-182 °C (HCl)

Stereochemistry: 2 sets of diastereomers each of which contains an enantiomeric pair.

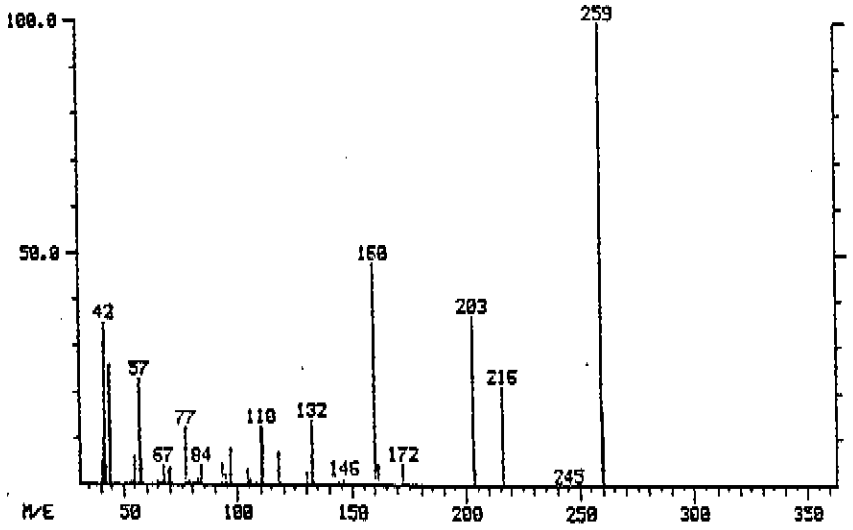
Thin-Layer Chromatography. System K - Rf 0.65.

Mass Spectrum.

Cis Isomer



Trans Isomer



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MEPERIDINE ANALOGUES

GENERAL STATEMENT OF THE PROBLEM

Several reversed ester analogues of meperidine have been clandestinely produced, distributed and abused as heroin substitutes in the United States and Canada since the late 1970's. This class of synthetic narcotic analgesics, also called prodine analogues because of their structural relationship to prodine, contains substances which are up to 3200 times more potent than meperidine as analgesics. The analogues identified in the illicit drug traffic to date are 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), 1-(2-phenethyl)-4-phenyl-4-acetoxypiperidine (PEPAP) and 1-(3-oxo-3-phenylpropyl)-4-phenyl-4-propionoxypiperidine (OPPPP). Clandestine production of MPPP produced the neurotoxic by-product, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). As a result, a number of cases of severe irreversible Parkinsonism, a central nervous system disorder affecting movement, have been reported in MPPP/MPTP abusers.

GENERAL HISTORY

Legitimate Use

Meperidine was originally prepared and introduced as a potent analgesic in the 1930's. Currently it is used for the relief of moderate to severe pain particularly in obstetrics and post-operative situations.

Reversed ester analogues of meperidine were synthesized in the 1940's and found to be more active analgesics than their meperidine counterparts. Alphaprodine which is intermediate in analgesic potency between meperidine and morphine is used infrequently as an analgesic in obstetrics, urologic examinations and procedures and preoperatively in major and minor surgery. None of the clandestinely produced analogues (MPPP, PEPAP, OPPPP) have been used clinically. MPTP, the neurotoxic by-product of the synthesis of MPPP, is used as an intermediate in chemical synthesis and is available commercially (Aldrich Chemical Company, Milwaukee, Wisconsin, USA, Cat. #19,991-5 and #14,219-0).

Illicit Use

Pharmaceutical preparations of meperidine and its clinically useful reversed ester analogues have been diverted and abused for many years, most frequently by members of the medical profession.

The clandestine synthesis and abuse of prodine analogues were first noted in 1976 when a 23 year old narcotic addict synthesized MPPP for personal use. Intravenous self-administration of MPTP-contaminated MPPP produced Parkinsonism in this individual. Treatment with anti-parkinson medications (l-dopa/carbidopa and bromocryptine) was successful in reducing his symptoms until his drug overdose death a few years later. Further episodes of MPPP/MPTP abuse occurred in the Western United States and Canada in the 1980's. Abusers developed irreversible Parkinsonism in both situations.

The identification of clandestinely produced 1-phenethyl-4-phenyl-4-acetoxypiperidine (PEPAP) was reported in 1984. Clandestine laboratories producing 1-(3-oxo-3-phenylpropyl)-4-phenyl-4-propionoxypiperidine (OPPPP) were reported in Canada and the United States in 1988. MPTP analogue by-products formed during the synthesis of PEPAP and OPPPP have been identified but do not produce MPTP-like neurotoxicity. There have been no reports of the clandestine synthesis or abuse of prodine analogues since 1988. The number of possible analogues, their ease of synthesis and relatively high potency, however, make recurrence a distinct possibility.

PHARMACOLOGY

General Effects

Meperidine produces characteristic morphine-like analgesia in humans with 60-100 mg equally effective to 10 mg morphine depending on the route of administration. It differs from morphine in its shorter duration of action and reduced antitussive and antidiarrheal actions. Meperidine produces respiratory depression, euphoria, tolerance and physical dependence and is recognized as a morphine-like opiate by narcotic addicts. Alphaprodine exhibits similar properties to those of meperidine in man but with increased analgesic potency and shorter duration of action. Both substances bind to opioid receptors and are predominantly mu-agonists.

The pharmacology of the reversed ester analogues, including MPPP, PEPAP and OPPPP, has not been studied in man. Animal studies, however, show that each is a more potent analgesic than morphine but with a shorter duration of action. MPPP and PEPAP substitute completely for morphine in morphine dependent monkeys and naloxone challenges precipitate withdrawal.

Structure-Activity Relationships

Both meperidine and its reversed esters (prodines) belong to the 4-phenylpiperidine class of substances. The reversed ester structure (OCOalkyl on the 4-position of the piperidine ring) of the prodines increases analgesic potency relative to the comparable meperidine compounds (COOalkyl on the 4-position of the piperidine ring) several fold. Otherwise the structure-activity relationships are comparable for meperidine and prodine analogues. A phenyl group at the 4-position of the piperidine ring is essential for morphine-like analgesia. The propionoxy ester compounds have the greatest analgesic activity in the reversed ester series. Substitution of an alkyl group into the 3-position of the piperidine ring further enhances analgesic activity. Analgesic potency increases with methyl, ethyl, butyl and allyl substituents but analgesic activity is abolished with large groups such as benzyl. Substitutions on the nitrogen of the piperidine have yielded analogues with analgesic potencies several thousand times that of meperidine.

Routes of Administration and Dosage Forms

Clandestinely produced prodine analogues are generally self-administered by intravenous injection. There has been one report of intranasal administration by an individual in Canada. These analogues have been distributed under the name "synthetic heroin" and are packaged in the same manner as heroin (eg., plastic bags, foil packets, balloons, capsules, etc.). The material ranges from a white crystalline powder to a brown granular substance. Samples are usually diluted ("cut") with lactose or other sugars. Concentration of the active analogue has

ranged from 0.3% to 27%. A few samples of almost pure MPTP have been identified in the illicit drug traffic. These have been associated with the most severe cases of Parkinsonism.

Pharmacokinetics

The following information is derived from studies involving meperidine and alphaprodine. Because of structural and chemical similarities, the analogues are likely to exhibit related pharmacokinetic profiles.

Meperidine and alphaprodine are rapidly absorbed from parenteral sites. Peak plasma concentrations of meperidine are obtained in 12 minutes after intravenous administration, and between one and two hours after oral administration. The half-life for meperidine after intravenous administration is between 2.4 and 4 hours for a therapeutic dose and up to 11 hours in individuals with cirrhosis of the liver. Peak plasma levels of alphaprodine are observed very quickly after intravenous administration with a half-life of 2.2 hours. Both meperidine and alphaprodine are rapidly distributed from plasma into the liver, kidney and muscle. The rapid initial decline in plasma concentration is followed by a slower distribution with a half-time of about 3 hours for meperidine. Approximately 60-75% of meperidine in plasma is protein bound. Alphaprodine disappears from plasma at a faster rate than meperidine.

Meperidine is metabolized primarily in the liver. It is hydrolyzed to meperidinic acid which is partially conjugated. It is also N-demethylated to the active metabolite normeperidine which may also be hydrolyzed and conjugated. The tremors, muscle twitches, hyperactive reflexes and convulsions seen after repeated administration of large doses of meperidine are associated with the accumulation of normeperidine. Very little is known about the metabolism of alphaprodine in man. In dogs, it is rapidly demethylated to noralphaprodine. The pharmacological activity of this metabolite has not been reported.

Very little meperidine (5-7 %) and normeperidine (5-17 %) are excreted unchanged in the urine; acidic (65 %) and other metabolites account for the remainder. The elimination half-life of alphaprodine is approximately 2 hours compared with approximately 4 hours for meperidine.

TOXICOLOGY

There have been relatively few reports of deaths from acute overdose of meperidine and alphaprodine and none due to the abuse of the clandestinely produced analogues of meperidine. Of particular concern, however, is the development of drug-induced Parkinsonism in individuals who have self-administered MPPP contaminated with MPTP.

Toxic Clinical Manisfestations of Drug Use and Overdose

Classical signs and symptoms of narcotic overdose (constricted pupils, respiratory depression, coma) are seen after acute poisoning with meperidine, alphaprodine and their analogues. Convulsions, particularly from meperidine, are more common than with other opiates. Death is nearly always due to respiratory failure. Accumulation of the normeperidine metabolite after repeated large doses of meperidine may produce twitching, tremors, mental confusion, hallucinations and tonic-clonic seizures. Daily doses of 3 grams or more of meperidine are associated with myoclonic jerks or generalized convulsions.

Individuals who have used MPPP contaminated with MPTP may exhibit some or all of the major clinical features of Parkinson's disease: generalized slowing and difficulty in moving, rigidity, resting tremor, flexed posture, and loss of postural reflexes. Some cases of MPTP-induced Parkinsonism have been misdiagnosed as catatonic schizophrenia. Early symptoms after use of MPTP include burning sensation on injection, visual hallucinations, jerking of limbs, stiffness, facial seborrhea and drooling. Cerebrospinal fluid in patients with MPTP-induced Parkinsonism contains markedly depressed levels of homovanillic acid (HVA) and normal or slightly elevated levels of 5-hydroxyindolacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylethylene glycol (MHPG). These findings are consistent with a selective destruction of dopaminergic neurons.

MPTP through its conversion into 1-methyl-4-phenylpyridine (MPP+) by the enzyme monoamine oxidase "B" (MAO "B") is responsible for the development of this drug-induced Parkinsonism. MPP+ acts to deplete dopamine in dopaminergic neurons and selectively destroys these neurons in a region of the substantia nigra.

Ironically MPTP was investigated for possible clinical use as an antiparkinsonism agent in the 1950s. Clinical trials were abandoned after two of the six human subjects died. MPTP was implicated in the early development of Parkinsonism in an organic chemist who synthesized the substance for several years as an intermediate. This case is particularly noteworthy since it may represent an example of MPTP toxicity through cutaneous absorption or vapor inhalation. MPTP may enter the body via absorption through the skin or eyes, injection, inhalation of vapor, powder, or contaminated particles and ingestion. Formation of a non-volatile, crystalline salt (bitartrate is good) is desirable to minimize handling of MPTP in laboratory settings.

The first case of MPTP toxicity due to abuse of the meperidine analogue MPPP occurred in 1976. During a six-month period in 1982 in northern California, seven individuals who were intravenously abusing "synthetic heroin" (MPPP with MPTP by-product) were seen by emergency room physicians with symptoms consistent with Parkinson's disease. It has been estimated that at least 400 individuals have used MPPP contaminated with MPTP. There is concern that these individuals who are currently asymptomatic may not be able to tolerate normal aging and will become symptomatic in time.

A study of the known users of MPPP/MPTP in northern California in 1982-3 showed that the average age was 28.2 (range of 21-48) years. Average daily use was 0.85 g (range of 0.1-2.0 g). Total amounts used ranged from an estimated 0.5 g (only 1-2 injections) to 240 g.

Forensic Toxicology

Autopsy Findings

Autopsy findings in meperidine and prodine overdose victims are similar to those of heroin and other narcotic overdose victims. Evidence of scarring at the injection sites and severe fibrosis of muscle tissues from repeated administration are possible. Neuropathological examinations of individuals who have used MPTP may show neuronal loss and gliosis in the zona compacta region of the substantia nigra. Rounded "Lewy" body structures may be seen.

Blood and Tissue Levels

The estimated lethal dose of meperidine in man is one gram. Blood levels of meperidine in meperidine overdose victims have been reported to be between 1.0 mg/L and 8.0 mg/L after intravenous administration; normeperidine levels ranged up to 7.0 mg/L. Both meperidine and normeperidine contribute to the toxic effects of the drug; both should be measured. Normeperidine has one-half the analgesic activity of meperidine, is more active as an anti-convulsant and appears to be two to three times more toxic. The identification of significant quantities of normeperidine in the blood suggests that meperidine was taken some time before the analysis. Combined meperidine/normeperidine blood concentrations greater than 3.0 mg/L coupled with substantial concentrations in other specimens are a good indication of a meperidine overdose.

Liver concentrations of meperidine in acute overdose victims have been reported as low as 2.0 mg/kg but are generally above 5.0 mg/kg. Normeperidine concentrations again should also be considered and have been reported up to 12.0 mg/kg. Several meperidine fatal overdose victims had between 2 and 10 mg of meperidine in their gastric contents.

Urine specimens of meperidine overdose victims also contain both meperidine and normeperidine. Meperidine and normeperidine concentrations ranged from 2.0 mg/L to over 60 mg/L.

An individual who died of an acute alphaprodine overdose had the following concentrations of alphaprodine: blood (3.3 mg/L); brain (10 mg/kg); liver (12 mg/kg); urine (21 mg/L); and gastric contents (0.15 mg).

CLINICAL MANAGEMENT

Treatment of acute overdose of meperidine and its analogues includes administration of oxygen and a narcotic antagonist (naloxone) and respiratory supportive measures. Naloxone may precipitate an acute withdrawal syndrome in patients who are physically dependent on narcotics and should be administered with caution. Naloxone antagonizes the opiate effects (sedation, respiratory depression, coma) but it does not antagonize the tremors or seizures caused by accumulation of normeperidine. Seizures and hallucinations may be treated with anticonvulsants (diazepam, phenytoin). Treatment of MPTP-induced Parkinsonism includes L-dopa and carbidopa (Sinemet) therapy. Additional dopamine agonists (e.g., bromocryptine) are also effective.

CLANDESTINE SYNTHESIS

For the purpose of discussing synthetic pathways, it is more efficient to think of the substances in this section as analogues of alpha-prodine, a reversed ester of meperidine. There are two general schemes for the synthesis of these substances, both of which proceed through a 4-hydroxy-4-phenyl-N-alkylpiperidine intermediate. For MPPP this intermediate is 4-hydroxy-4-phenyl-N-methylpiperidine. Both the intermediate and final products in the synthesis of MPPP are easily dehydrated by excess heat or acid to form MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). **CAUTION!!!** MPTP produces an irreversible Parkinson-like syndrome in humans after exposure to small quantities. It has been implicated as a cause of Parkinsonism in drug abusers who have self-

administered MPTP intravenously (Langston et al., 1983). There have also been at least two case reports of industrial chemists who developed symptoms of Parkinson's disease at unusually early ages after prolonged exposure to MPTP (Markey and Burns, 1984).

Synthesis I

An appropriate N-substituted-4-piperidone is treated with a Grignard reagent (arylmagnesium halide) to obtain the 4-piperidinol which is purified by distillation and recrystallization. The resulting intermediate is esterified with an acid anhydride or acid chloride to give the 4-phenyl-4-acyloxy ester. The appropriate 4-piperidones may be prepared by the addition of an alkylamine into acrylate or methacrylate esters followed by ring closure through a Dieckman condensation and subsequent hydrolysis and decarboxylation.

Synthesis II

Alpha-methylstyrene, formaldehyde and the appropriate alkylamine are reacted to form the intermediate 4-piperidinol which is esterified to produce the final product. OPPPP has been synthesized from 4-phenyl-4-piperidinol hydrochloride, paraformaldehyde and acetophenone via a Mannich reaction followed by acylation with propionyl chloride.

Precursors and Essential Chemicals

N-Methyl-4-piperidone or 1-(2-phenylethyl)piperidone (I)
Propionic anhydride/propionyl chloride or acetic anhydride/acetyl chloride (I, II)
Alpha-methylstyrene (II)
Formaldehyde or paraformaldehyde (II)
Methylamine or 2-phenethylamine (II)
4-Phenyl-4-piperidinol (II)
Acetophenone (II)
Phenylmagnesium bromide (Grignard reagent) or phenyl lithium (I)
Sodium methoxide (I)

ANALYTICAL CHEMISTRY

Body Fluids

No reports describing the identification of prodine analogues in body fluids were found in the literature.

Chromatography

Thin-Layer Chormatography

Analysis of meperidine and normeperidine in biological fluids and body tissues after extraction was reported by Siek (1978). It was suggested that dichloromethane be used in place of chloroform in final extractions of body fluids or tissues containing normeperidine due to the formation of an artifact normeperidine ethylcarbamate from normeperidine and ethyl chloroformate (Siek, 1978).

Gas chromatography

Gas chromatographic methods of analysis of meperidine and its normetabolite in biological specimens using flame ionization have been reported by Chan et al. (1974), Mather and Tucker (1974), Wainer and Stambaugh (1978) and Siek (1978). Use of nitrogen-phosphorus detection was reported by Jacob et al. (1982) and the use of electron capture detection was reported by Hartvig and Fagerlund (1983). Derivatization of the normeperidine metabolite prior to gas chromatographic analysis is common (Siek, 1978; Hartvig and Fagerlund, 1983).

Liquid Chromatography

The use of high pressure liquid chromatography in the analysis of meperidine and normeperidine in serum and urine has been described by Meatherall et al. (1985).

Spectrometry

Electron impact mass spectral analysis of meperidine and its metabolites after gas chromatographic separation has been reported by Lindberg et al (1975), Siek (1978), Todd et al. (1979) and Verbeeck et al. (1980).

Quantitaion

Quantitation of meperdine and normeperdine using gas chromatography equipped with a flame ionization detector and utilizing mepivicaine as an internal standard was reported by Siek (1978). A similar method using benzphetamine as the internal standard was reported by Stambaugh et al (1976). The identification and quantitation of MPTP and MPP+ in brain tissue by combined gas chromatography and mass spectrometry were reported by Shih and Markey (1986).

Solid Dosage Forms

Melting Point Determinations

The melting points of the base and HCl forms of meperidine were obtained from Merck (1989). The melting points of the HCl forms of MPPP and PEPAP were reported by Gunn. Fries et al. (1986) provided melting points for MPTP HCl.

Colour Tests

The Marquis reagent can be used to screen for meperidine and MPPP (Moffat, 1986 and Gunn). The Mecke and cobalt thiocyanate reagents may be used to screen for MPPP while Liebermann's reagent may be used to screen for meperidine (Moffat, 1986 and Gunn).

Chromatography

Thin-Layer Chromatography

The following thin-layer chromatography systems were used:

System A. Chloroform : methanol (4:1), Merck Silica gel 60 F254. Visualization with iodoplatinate spray. (Heagy, 1982)

System B. Chloroform : Methanol (4:1), Merck Silica gel 60 F254. Visualization with marquis reagent streaked on plate. (Heagy, 1982)

Powders were extracted with methylene chloride for spotting. Rf values were measured to the center of the spot or streak and may vary with concentration (Heagy, 1982).

Additional References: Weingarten, 1988.

Gas Chromatography

The following GC systems were reported by Gunn:

System A

Column. 6 ft x 4 mm glass column packed with 3% OV-1 on 100/120 mesh Gas Chrom Q.
Column Temp. 190 °C.
Injector Temp. 260 °C.
Carrier Gas. Nitrogen at a flow rate of 49 ml/min.
Detector. Flame ionization.
Detector Temp. 312 °C.

System B

Column - 6 ft x 4 mm glass column packed with 3% OV-17 on 100/120 mesh Gas Chrom Q.
Column Temp. 190 °C.
Injection Temp. 260 °C.
Carrier Gas - Nitrogen at a flow rate of 51 ml/min
Detector - Flame ionization
Detector Temp. 312 °C.

Additional References: Heagy (1982), Mills (1987) and Weingarten (1988).

High Performance Liquid Chromatography

The following HPLC systems was used:

System A (Gunn)

Column - 3.9 mm x 30 cm stainless steel (Waters Part No. 27477) packed with Microporasil 10 m silica particles.
Mobile Phase - Solvent of cyclohexane 2520 ml, conc. ammonia 1.1 ml, methanol 216 ml, water-washed chloroform 863 ml with a flow rate of 1.0 ml/min
Detector - UV (254 nm)

System B (Gunn)

Column - Perkin Elmer HS5C18 column
Mobile Phase - 40% methanol and 60% phosphate buffer
Detector - UV (254 nm)

Spectroscopy/Spectrometry

Ultraviolet Spectroscopy

Ultraviolet spectral data were obtained in acidic and neutral solutions (Mills and Roberson, 1987). Values were reported as wavelengths of maximum absorbance recorded over a range of 220 to 340 nm.

Infrared Spectroscopy

The infrared spectrum of meperidine recorded from potassium bromide pellets was obtained from Mills and Roberson, (1987). The infrared spectra of the hydrochlorides of MPPP and MPTP were recorded from potassium bromide pellets (Gunn).

Additional References: Heagy (1982) and Weingarten (1988).

Mass Spectrometry

Electron impact (70 eV) mass spectra were obtained after gas chromatographic separation of the substances. The instruments (Finnigan 4000 and 4600) utilized a quadrupole mass analyzer. Mass spectrum of meperidine was obtained from Mills and Roberson (1987). The mass spectra of MPPP and MPTP were obtained from Gunn.

Additional References: Moffet (1986), Heagy (1982), Langston et al. (1983), and Weingarten (1988).

MEPERIDINE

CAS Registry Number: 57-42-1

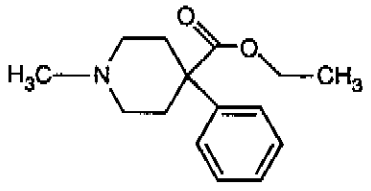
IUPAC Name: 1-Methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester

CA Index Name: 1-Methyl-4-phenyl-4-piperidinecarboxylic acid ethyl ester
1-Methyl-4-phenylisonipecotic acid ethyl ester

Other Names: N-Methyl-4-phenyl-4-carbethoxypiperidine
Ethyl 1-methyl-4-phenylpiperidine-4-carbethoxypiperidine
Isonipecaine
Pethidine

International Control: I, 1961 Convention

Chemical Structure:



M.F.: $C_{15}H_{21}NO_2$ **M.W.:** 247.35
$C_{15}H_{22}ClNO_2$ (HCl) 283.80 (HCl)

Physical Appearance: Meperidine HCl exists as minute crystals.

Chemical/Physical Properties

M.P.: 186-189 °C (HCl)

Solubility: HCl is soluble in water, acetone, and ethyl acetate; slightly soluble in alcohol and isopropanol; and insoluble in benzene and ether.

Stereochemistry: No diasteriomers or enantiomers

Colour Tests. Liebermann's Test - red-orange
Marquis - orange

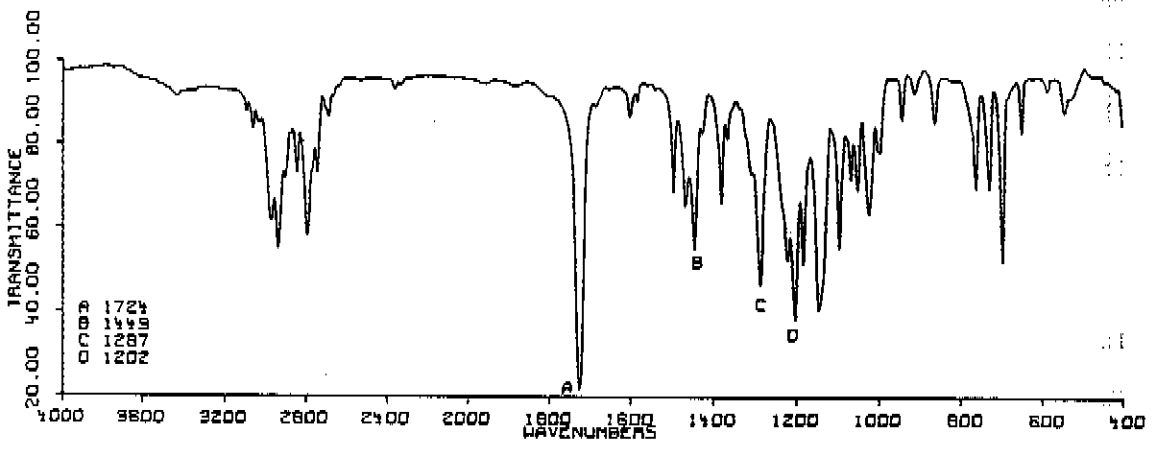
Gas chromatography. System A - RT 2.42 min; System B - RT 2.59 min

High Pressure Liquid Chromatography. System A - RT 5.77 min

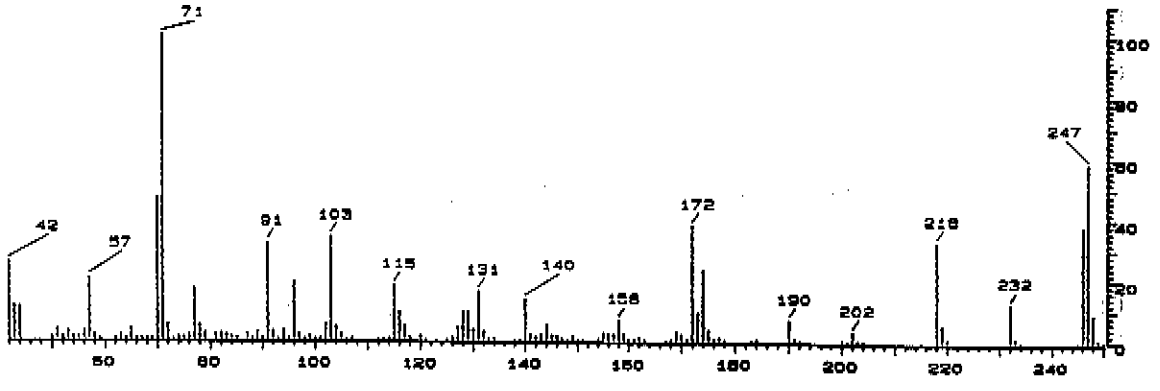
Ultraviolet Spectroscopy.

251 nm, 257 nm, 263 nm (acidic and basic solutions)

Infrared Spectrum



Mass Spectrum.



1-METHYL-4-PHENYL-4-PROPIONOXYPIPERIDINE

CAS Registry Number: 13147-09-6

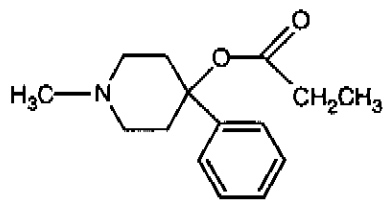
IUPAC Name: 1-Methyl-4-phenyl-4-piperidinol propionate (ester)

CA Index Name: 1-Methyl-4-phenyl-4-piperidinol propionate (ester)

Other Names: 1-Methyl-4-phenyl-4-piperidyl propionate
1-Methyl-4-phenyl-4-propionoxypiperidine
3-Demethylprodine
Desmethylprodine
MPPP

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{15}H_{21}NO_2$ **M.W.:** 247.35

Chemical/Physical Properties

M.P.: 185-187 °C (HCl)

Solubility: HCl is soluble in methylene chloride.

Stereochemistry: No diastereomers or enantiomers

Colour Tests. Marquis - red-violet to blood-red, dependant on concentration
Mecke - no colour
Cobalt thiocyanate - blue (chloroform soluble)

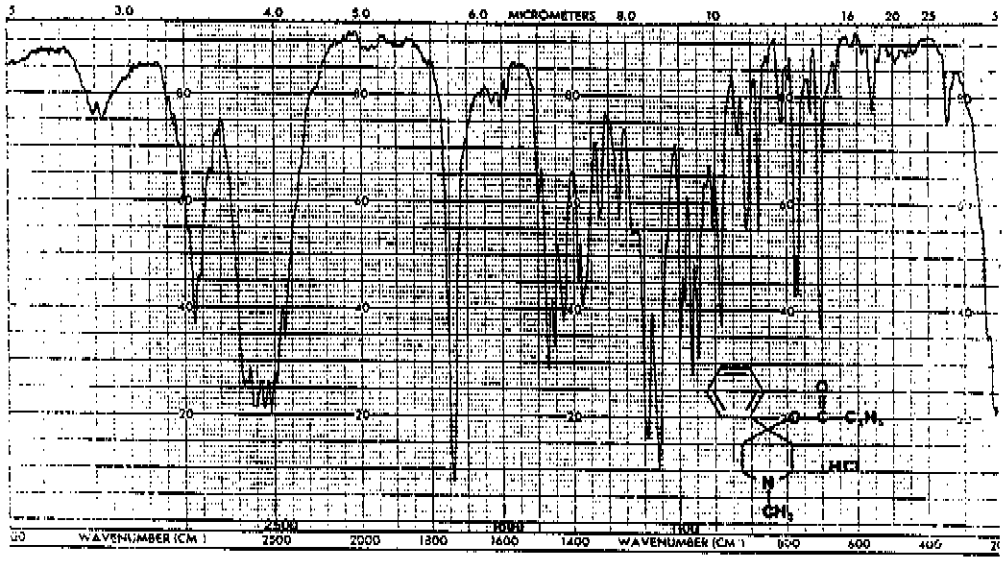
Thin Layer Chromatography. System A - RT 0.4 purple to purple brown (on drying); System B - RT 0.4 brown to red

Gas Chromatography. System A - RT 2.52 min; System B - RT 2.65 min

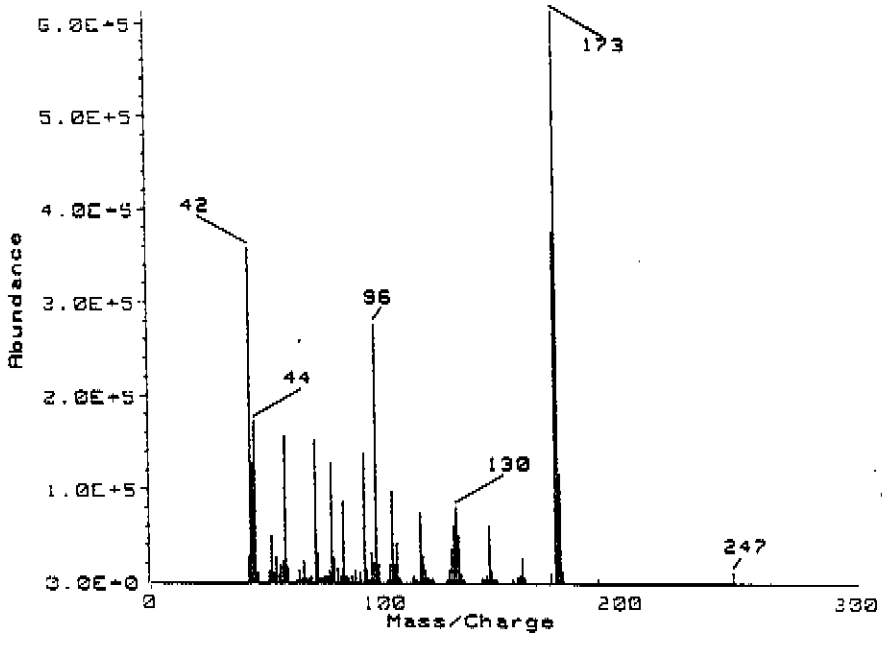
High Pressure Liquid Chromatography. RT 5.97 min

Infrared Spectrum.

HCl



Mass Spectrum.



1-METHYL-4-PHENYL-1,2,5,6-TETRAHYDROPYRIDINE

CAS Registry Number: 28289-54-5

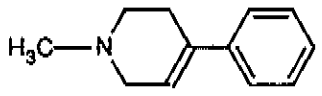
IUPAC Name: 1,2,5,6-Tetrahydro-1-methyl-4-phenylpyridine

CA Index Name: 1,2,5,6-Tetrahydro-1-methyl-4-phenylpyridine

Other Names: 1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine
MPTP

International Control: Not controlled

Chemical Structure:



M.F. $C_{12}H_{15}N$ **M.W.:** 173.26

Physical Appearance: Base and HCl are crystalline materials

Chemical/Physical Properties.

M.P.: 40-42 °C (base)
250 °C (HCl)

Thin Layer Chromatography. System A - RT 0.29 blue-black to purple (on drying); system B - RT 0.29 brown to red

Gas Chromatography. System A - RT 1.32 min.; System B - RT 1.25 min.

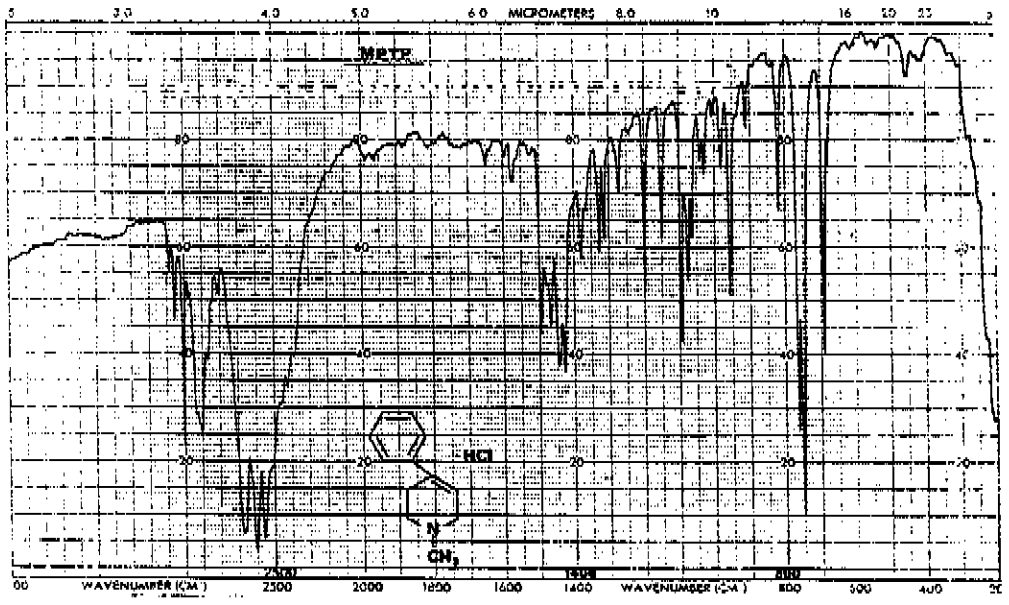
High Pressure Liquid Chromatography. RT 5.36 min.

Ultraviolet Spectroscopy.

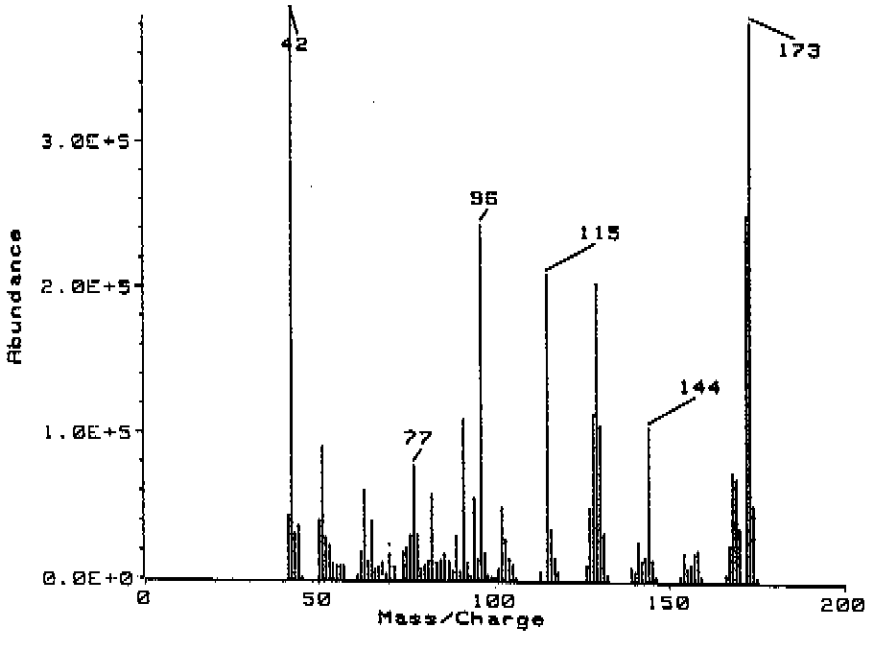
Acid solution - 242 nm
Basic solution - 248 nm

Infrared Spectrum.

HCl



Mass Spectrum.



1-(2-PHENETHYL)-4-PHENYL-4-ACETYLOXYPIPERIDINE

CAS Registry Number: 64-52-8

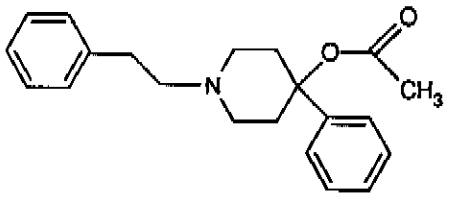
IUPAC Name: 1-Phenethyl-4-phenyl-4-piperidinol acetate (ester)

CA Index Name: 4-Phenyl-1-(2-phenylethyl)-4-piperidinol acetate (ester)

Other Names: 1-Phenethyl-4-phenyl-4-piperidyl acetate
PEPAP

International Control: I & IV, 1961 Convention

Chemical Structure:



M.F.: $C_{21}H_{25}NO_2$ **M.W.:** 323.44

Physical/Chemical Properties.

M.P.: 214 - 215.5 °C (HCl)

Solubility: HCl is soluble in methylene chloride.

Stereochemistry: No diastereomers or enantiomers

Gas Chromatography. System A - RT 3.91 min; System B - RT 5.02 min

High Pressure Liquid chromatography. RT = 10.4 min

Mass Spectrometry.

GCMS (electron impact) of PEPAP shows the base peak at 172, strong peak at 232, and smaller peaks at 105, 77, 91, 190, 56, 128 and 263 amu.

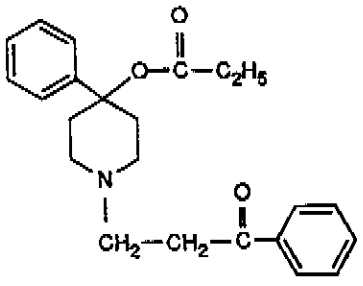
1-(3-OXO-3-PHENYLPROPYL)-4-PHENYL-4-PROPIONOXYPIPERIDINE

Chemical Name: 1-(3-Oxo-3-phenylpropyl)-4-phenyl-4-propionoxypiperidine

Other Names: OPPPP

International Control: Not controlled.

Chemical Structure:



M.F.: $C_{23}H_{27}O_3N$ **M.W.:** 365.48

Physical Apperance The HCl is a crystalline material.

Chemical/Physical Properties.

M.P.: 157.4-159 °C (HCl)

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AMFETAMINE ANALOGUES

GENERAL STATEMENT OF THE PROBLEM

Depending on how the molecular structure of amfetamine is modified, it can act as a potent psychomotor stimulant (e.g. methamfetamine), as a powerful hallucinogen (e.g. 4-bromo-2,5-dimethoxyamfetamine, DOB) or as a psychedelic agent (e.g. 3,4-methylenedioxymethamfetamine, MDMA). In recent years, clandestine chemists have attempted to exploit each of these possibilities. The result has been the appearance of a number of illicit "designer" synthetic amfetamine analogues on the street. Examples of such analogues include N,N-dimethylamfetamine (N,N-DMA), para-methoxymethamfetamine (PMMA), 3,4-methylene-dioxy-N-ethylamfetamine (MDEA), N-hydroxy-3,4-methylenedioxyamfetamine (N-OH-MDA), and 4-bromo-2,5-dimethoxyphenethylamine (2-CB).

Potentially, these amfetamine analogues pose a significant international public health problem. The reason for this is several fold. First, when manufactured illicitly, such analogues seldom, if ever, undergo potency testing. Hence, risk of human overdose is ever present. Second, underground chemists rarely test the purity of the drugs they manufacture with any rigor. Thus, risk of intoxication by a contaminant is real (as occurred with MPPP and MPTP - see Meperidine Analogue chapter). Third, a number of amfetamine analogues (e.g., some of the ring-substituted amfetamine derivatives as well as methamfetamine) have recently been shown to be toxic to brain dopamine and serotonin nerve cells in animals. Humans experimenting with such analogues may therefore run the risk of incurring neurological impairment.

GENERAL HISTORY

Legitimate Use

Amfetamine, the parent compound for virtually all of the analogues to be discussed, was synthesized around the turn of the century. Throughout the world, amfetamine has been used (with variable success) to treat narcolepsy, depression, obesity, hypno-sedative drug overdose and minimal brain dysfunction or hyperkinesis in children. It has also been used in an effort to improve human cognitive performance. A number of legitimate amfetamine derivatives are now in use as nasal decongestants (e.g., phenylpropanolamine) and appetite suppressants (e.g., fenfluramine).

With regard to synthetic amfetamine analogues, particularly ring-substituted amfetamines such as MDA and MDMA, they have no widely accepted medical utility. MDMA is said to have undergone trials as an anorectic agent. However, these reports are difficult to substantiate. More recently, a small number of mental health professionals in the United States and Europe have suggested that MDMA may be useful as a psychotherapeutic adjunct. To date, however, this suggestion has not been validated through the use of double-blind, placebo-controlled studies.

Illicit Use

Nonmedical use of amfetamine and its various congeners began almost as soon as their therapeutic use. To both physicians and patients alike, it quickly

became apparent that the mood-elevating or stimulant effects of amfetamines were subject to exploitation. By 1960, an epidemic of methamfetamine abuse had taken place in Japan. Similar widespread methamfetamine abuse occurred in the United States in the 1960s and early 1970s. Illicit use of amfetamines, particularly dextroamfetamine and methamfetamine, continues to be a problem not only in North America and the Orient, but also in Europe and Australia. Recently, a novel form of methamfetamine abuse has appeared in Hawaii and California. It involves the inhalation of the dextro isomer of methamfetamine HCl, which on the street is being called "Ice".

Another amfetamine analogue that has recently been identified in the drug culture of the United States is the N-methylated form of methamfetamine. Clandestine laboratory operators, with some difficulties in obtaining ephedrine because of precursor regulation, purchased N-methylephedrine and used it in place of ephedrine in their methamfetamine synthesis. This analogue, N,N-dimethyl-amfetamine (N,N-DMA), appears to be approximately 5-10 times less potent than methamfetamine, at least in animal studies. While there is some indication that on the street N,N-DMA may be used at higher doses than methamfetamine (to compensate for its reduced potency), further confirmation of this point is needed. Law enforcement officials in Japan have also identified N,N-DMA in drug evidence submissions.

Another group of amfetamine derivatives frequently being identified in the illicit drug market is the so called "ring-substituted" group of amfetamines. This group consists of MDA (known as the "love drug" in the 1970s), MDMA ("Ecstasy", "ADAM"), and 3,4-methylenedioxyethylamfetamine (MDEA, "Eve"), N-hydroxy-3,4-methylenedioxyamfetamine (N-OH-MDA), para-methoxymethamfetamine (PMMA) and 4-bromo-2,5-dimethoxyphenethylamine (2-CB). A notable feature of some or most of these drugs is that in addition to variable amounts of psychomotor stimulation, they induce psychotomimetic effects (for example 2-CB, DOM). MDA and MDMA are said to induce a psychedelic state characterized by expanded emotional insight and empathy. Chemically, ring-substituted amfetamines such as MDA and MDMA can be viewed as hybrids of amfetamine, the prototypic stimulant, and mescaline, the prototypic hallucinogen. Illicit use of MDA, MDMA and related compounds has been reported in North America, South America, Europe, Australia and Japan. It is important to note that these are only a few of the many active amfetamine analogues which may be easily produced in clandestine laboratories.

PHARMACOLOGY

General Effects

Like amfetamine, almost all of the amfetamine analogues can be regarded as "sympathomimetic amines". The reason for this is that many of their pharmacological effects result from activation of the sympathetic portion of the autonomic nervous system. In particular, most amfetamine analogues increase heart rate, stimulate respiration, enhance locomotor activity, reduce thirst, diminish appetite, decrease fatigue and elevate mood and cause insomnia. In addition, many of the ring-substituted amfetamines such as DOB and DOM also induce hallucinations. Finally, the psychedelic effects of MDMA and related ring-substituted amfetamines (MDA and MDEA) have been mentioned above. Trismus or jaw clenching is a frequent side-effect of many of these drugs.

Most, if not all, of the pharmacological effects of "stimulant" amfetamine analogues such as N,N-DMA are thought to be mediated by brain monoamines (dopamine, norepinephrine and serotonin). These drugs augment monoaminergic

neurotransmission by: 1) releasing monoamines into the synaptic cleft, 2) blocking their re-uptake inactivation and 3) inhibiting monoamine oxidase (MAO), the enzyme that normally degrades monoamines. It is only recently that the pharmacology of MDMA and other ring-substituted amfetamines has come under careful scrutiny. To date, the bulk of the evidence suggests that the sympathomimetic effects of these drugs are also likely to be mediated by catecholamines in the brain and in the periphery. In addition, there is evidence to suggest that serotonergic systems may be involved in the central effects of these drugs. A unique mechanism or central site of action for MDMA and related drugs (MDA, MDEA) has also been postulated.

Structure Activity Relationships

To discuss the structure activity relationships (SAR) of illicit synthetic amfetamine analogues, it is helpful to recall that the key structural determinants of amfetamine's activity are its: 1) unsubstituted phenyl ring, 2) alpha methyl group, 3) primary amino group and 4) two-carbon side-chain (connecting the phenyl ring and the primary amino group).

N-alkylation of amfetamine with anything other than a methyl group (as in N-methylamfetamine or methamfetamine) tends to attenuate its psychomotor stimulant activity. Thus, N-ethylamfetamine and N-propylamfetamine are less potent psychomotor stimulants than amfetamine or methamfetamine. Di-alkylation of amfetamine's primary amino group (as in N,N-DMA) appears to cause a similar effect since, in animals at least, N,N-DMA is 5-10 times less potent than methamfetamine. Other alterations which reduce the psychomotor stimulant activity of the amfetamine molecule include 1) removal of its alpha methyl group (as in 2-CB), 2) deamination or 3) multiple ring substitutions.

Multiple substitutions on the phenyl ring of amfetamine not only attenuate its psychomotor stimulant activity, they also tend to confer hallucinogenic activity onto the molecule. Thus, 4-methyl-2,5-dimethoxyamfetamine (DOM), 4-bromo-2,5-dimethoxyamfetamine (DOB) and 3,4,5-trimethoxyphenethylamine (mescaline) are all potent hallucinogenic agents. 4-Chloro-2,5-dimethoxyamphetamine, a drug that has recently been identified in the United States' illicit drug market, may also have this property. In animals, phenylalkylamines lacking or having only one substituent on the phenyl ring (such as para-methoxyamfetamine, PMA) do not substitute for DOB in animal drug discrimination paradigms, suggesting that they do not have hallucinogenic activity. Ring-substituted amfetamines lacking the alpha methyl group (such as 2-CB) also tend to have reduced hallucinogenic or DOB-like activity in animals.

Placement of a methylenedioxy moiety on the 3 and 4 positions of amfetamine's phenyl ring gives rise to 3,4-methylenedioxyamfetamine or MDA, a compound which (as alluded to above) appears to have a unique psychopharmacological profile of action. Whether this profile results from a blend of psychomotor stimulant and hallucinogenic effects, or whether it is due to some other drug action is not yet known. Other amfetamine analogues with MDA-like properties include 3,4-methylenedioxymethamfetamine (MDMA), 3,4-methylenedioxyethylamfetamine (MDEA) and N-hydroxy-3,4-methylenedioxyamfetamine (N-OH-MDA). Of these MDA and MDMA appear to be the most potent.

When optical isomers are considered, the dextro isomers of amfetamine analogues tend to have greater psychomotor stimulant actions than the levo isomers. By contrast, the levo isomers of DOB, DOM and other such congeners tend to have greater hallucinogenic potency than the dextro isomers.

Dosage Forms and Routes of Administration

Most amfetamine analogues on the street consist of the racemic mixture of the drug. They are usually sold as white or off-white powders, and sometimes come in tablet or capsule form. Amfetamine and methamfetamine are generally taken at a dose of 5-10 mg orally. N,N-DMA, which is less potent, is said to be taken in higher doses. MDA, MDMA and other ring substituted amfetamines are available as powders, tablets and capsules. The usual psychotropic dose of MDMA, MDA and N-OH-MDA ranges from 80 to 125 mg. Most often these drugs are taken orally. However, they can also be inhaled and injected intravenously. "Hallucinogenic" amfetamines such as DOM and DOB are generally taken by mouth and used in lower doses (15-25 mgs). "Ice" or (+)-methamfetamine HCl is typically self-administered by means of inhalation. Dosages are uncertain.

It is important to emphasize that dose will vary depending on the particular amfetamine analogue in question, its dosage form, the route of administration, and the drug history of the individual. For example, in a drug naive subject, 100-125 mg dose of MDMA may have profound subjective effects. By contrast, in a tolerant individual, the same dose may be without much effect. Often tolerant subjects can ingest extremely high doses of MDMA (300-500 milligrams), doses which might prove lethal in a drug naive subject.

Pharmacokinetics

Because of their high lipid solubility (or predicted pKa), most amfetamine analogues, when taken orally, are readily absorbed from the gastrointestinal tract. Once in the bloodstream, they quickly distribute to the various body compartments and cross the blood brain barrier. Within minutes of administration, the central effects of most amfetamine derivatives are reliably identified. The half-life of amfetamine analogues in human plasma will depend on its dosage form, how much was taken and how it was administered. For a 5-10 mg dose of dextroamfetamine taken orally, the plasma half-life is approximately 8-10 hours. The plasma half-life for most illicit synthetic amfetamine derivatives has not been determined.

Metabolism of N-substituted amfetamines (such as N,N-DMA)proceeds largely by one of two routes. The first involves para hydroxylation of the phenyl ring; the second involves N-dealkylation, deamination and subsequent oxidation of the amfetamine's side chain. In man, the second pathway predominates. Little is known about the metabolism of MDMA and other ring-substituted amfetamines in either experimental animals or man. Some recent preliminary findings suggest that MDMA, like methamfetamine, undergoes N-dealkylation and is converted to MDA. The latter then undergoes oxidative cleavage of its methylenedioxy ring substituent and O-dealkylation and is eventually converted largely to alpha-methyldopamine and 3-methoxy-alpha-methyldopamine. To what extent these and other metabolites such as 3-hydroxy-4-methoxymethamfetamine, 4-hydroxy-3-methoxymethamfetamine and 3,4-dihydroxymethamfetamine contribute to the activity of MDMA and MDEA is not yet clear.

Elimination of amfetamine and methamfetamine (and probably N,N-DMA) is chiefly by renal excretion, which varies with urine flow and pH. N-alkylated amfetamines are also excreted in saliva and sweat, though in small amounts. Acidification of the urine and vigorous hydration (so as to promote increased urine output) increase the renal excretion of N-alkylated amfetamines. Elimination of ring-substituted amfetamines also appears to be by renal excretion. The hydroxylated metabolites of MDMA are excreted in the urine as O-glucuronide or O-sulfate conjugates.

TOXICOLOGY

Toxic Clinical Manisfestations of Drug Use and Overdose

In large part, the toxic effects of amfetamine analogues can be viewed as an exaggeration of their pharmacological actions. As such, they largely reflect over-stimulation of the peripheral sympathetic and central nervous systems. Signs and symptoms of acute amfetamine intoxication typically include flushing, sweating, tachycardia (sometimes resulting in life-threatening arrhythmias), hypertension (occasionally resulting in intracerebral hemorrhage) and sometimes convulsions and severe hyperthermia. The latter is said to be the most common cause of death in amfetamine overdose. Hyperactivity, restlessness, bellicosity and confusion are also often observed, particularly with the "stimulant" amfetamines such as (+)-methamfetamine. Not uncommonly, acute intoxication with amfetamine and some of its analogues results in paranoid ideation, a mental state which some have likened to paranoid schizophrenia. In general, psychosis clears soon after the drug is discontinued. Monoamine oxidase inhibitors potentiate the toxic effects of amfetamine and its various analogues.

The manifestations of chronic intoxication with amfetamine and related drugs resemble those of acute amfetamine overdose. However, marked weight loss and persistent psychiatric disturbance may develop.

The toxicology of N-substituted and ring-substituted amfetamines tends to parallel that of the parent compounds, probably because they retain much of their pharmacological activity. In the case of PMA, MDA, MDMA and MDEA, a number of deaths have been reported. In some of these cases, high levels of the drug have been found at the time of autopsy. In other instances, there has been insufficient clinical or forensic information to permit accurate ascertainment of the immediate cause of death. Severe intoxication with MDMA in a patient taking a monoamine oxidase inhibitor (phenelzine) has been reported. It is not yet known if the serotonergic neurotoxic effects of MDA, MDMA and MDEA which have been well documented in animals also occur in humans. Of note, however, is the fact that the neurotoxic dose of MDMA in nonhuman primates closely approaches that typically taken by man.

Forensic Toxicology

The most consistent pathologic finding at autopsy of cases of amfetamine overdose is cerebrovascular hemorrhage. In a limited number of cases there is evidence of left ventricular failure with pulmonary edema. In these cases, it is often surmised that the drug induced a cardiac arrhythmia (ventricular fibrillation). Other less consistent findings at autopsy include cerebral hyperemia, necrotizing angiitis, cerebral edema, hydrocephalus, hepatic and renal damage. How many of these findings are coincidental, and how many are related to aseptic drug use is unclear.

With regard to the forensic toxicology of ring-substituted amfetamine analogues, relatively little is known. In the cases thus far reported, there have been no consistent pathologic findings. The most common cause of death invoked is cardiac arrhythmia, though definitive proof is often lacking. Tissue levels of MDA, MDMA and related drugs determined at autopsy have a wide range. For example, in an MDA fatality, tissue levels of MDA ranged from 0.23 mg/ 100 ml in blood to 17.5 mg/ 100 ml in urine. In five fatalities associated with the use of MDEA and MDMA, blood levels ranged from 0.09 mg/ 100 ml to 0.2 mg/100 ml. The highest levels of MDEA were found in the kidney (4.5 mg/kg of tissue).

CLINICAL MANAGEMENT

In the emergency room, the management of intoxication with amfetamine and related psychomotor stimulant drugs is symptomatic and involves the use of a dopamine receptor antagonist (e.g., chlorpromazine or haloperidol) to combat the central effects of the drug. It also involves the use of a peripheral alpha-receptor blocker (e.g., phentolamine) to counteract the drug's hypertensive effects. In addition, the patient should be hydrated and the urine should be acidified by administering ammonium chloride to promote excretion of the drug in the urine. Measures to lower body temperature should also be implemented. Gastric lavage is sometimes recommended, but of doubtful utility because most amfetamines are rapidly absorbed from the gastrointestinal tract.

The management of MDA, MDMA, MDEA overdose should proceed along similar lines. Recently, the suggestion has been made that serotonin uptake inhibitors such as fluoxetine might also be of use in cases of MDMA intoxication (to protect central serotonin neurons). However, at present there is insufficient clinical experience with this mode of intervention to warrant its routine implementation.

CLANDESTINE SYNTHESIS

Synthesis of Methylenedioxyamfetamines

Synthesis I

The N-substituted methylenedioxyamfetamines can be synthesized by the reductive amination of 3,4-methylenedioxyphenyl-2-propanone (piperonylacetone) using sodium cyanoborohydride as the reducing agent. Piperonylacetone can be synthesized from isosafrole, hydrogen peroxide and formic acid or from safrole, mercuric chloride and hydrobromic acid. Variation of the amine provides for the synthesis of several N-substituted compounds.

Synthesis II

Condensation of piperonal with nitroethane forms 3,4-methylenedioxyphenyl-2-nitropropene which is reduced to MDA with lithium aluminum hydride. Acylation of MDA followed by hydride reduction results in other MDA analogues.

Precursors and Essential Chemicals

3,4-Methylenedioxyphenyl-2-propanone (I)
Formamide/ammonium formate or methylamine or ethylamine or hydroxylamine (I)
Safrole (I)
Isosafrole (I)
Piperonal (II)
Nitroethane (II)
Formic acid or acetic anhydride (II)
Sodium cyanoborohydride (I)
Lithium aluminum hydride (II)
Hydrogen peroxide (I)
Hydrogen bromide (I)
Mercuric chloride (I)
Ammonium acetate (II)
Acetic acid (II)

Synthesis of Para-Methoxymethamfetamine (PMMA)

Synthesis I

PMMA can be prepared via a Leuckart reaction using 4-methoxyphenylacetone and N-methylformamide followed by hydrolysis of the N-formyl intermediate.

Synthesis II

Another method involves the acylation of PMA with ethyl chloroformate in the presence of triethylamine followed by reduction of the carbamate.

Precursors and Essential Chemicals

4-Methoxyphenylacetone (I)
N-Methylformamide (I)
4-Methoxyamfetamine (II)
Ethyl chloroformate (II)
Hydrochloric acid (I)
Triethylamine (II)
Sodium cyanoborohydride (II)

Synthesis of 4-Bromo-2,5-dimethoxyphenethylamine (2-CB)

4-Bromo-2,5-dimethoxyphenethylamine is prepared by the condensation of 2,5-dimethoxybenzaldehyde with nitromethane to form 2-nitro-1-phenylpropene (2,5-dimethoxy-beta-nitrostyrene) followed by reduction with lithium aluminum hydride and bromination with bromine in acetic acid. Direct bromination of 2,5-dimethoxyphenethylamine using bromine in acetic acid has also been reported.

Precursors and Essential Chemicals

2,5-Dimethoxybenzaldehyde
Nitromethane
Bromine
Lithium aluminum hydride
Acetic acid

Synthesis of N,N-Dimethylamfetamine (N,N-DMA)

N,N-dimethylamfetamine is prepared by the reduction of N-methylephedrine with hydriodic acid in the presence of red phosphorus. This is a modification of a commonly used methamfetamine synthesis. The diasteriomers (-)-ephedrine and (+)-pseudoephedrine reduce to (+)-N,N-dimethylamfetamine. The diastereomers (+)-ephedrine and (-)-pseudoephedrine reduce to (-)-N,N-dimethylamfetamine while the racemic mixture of either ephedrine reduces to racemic N,N-dimethylamfetamine.

Precursors and Essential Chemicals

N-Methylephedrine or N-methylpseudoephedrine
Hydriodic acid
Red phosphorus

ANALYTICAL CHEMISTRY

Body Fluids

Urine should be the biological sample of choice for testing purposes. It is generally the most easily accessible biological fluid in which drugs and their metabolites are excreted and/or concentrated, thus increasing the chances for their detection. For all the drugs considered in this chapter, a significant amount of the administered dose is excreted unchanged in urine; therefore, detection of their use by urinalysis will normally involve analysis for the parent drug.

Schemes for the extraction of substances considered in this chapter have been described by Hornbeck and Czarry (1989), Gubitz and Wintersteiger (1980), Shimosato et al. (1986), Logan et al. (1990) and Chen et al. (1990).

Immunoassay

Most immunoassays for amfetamine-like drugs are designed for the detection of amfetamine and/or methamfetamine. However, some of the immunoassays (used according to the manufacturer's instructions) show significant cross-reactivity with some of the ring-substituted amfetamine analogues (Ruangyuttikarn and Moody, 1988; Kunsman et al., 1990; Cody, 1990). Because immunoassays are not compound specific, positive results must always be confirmed by a second more specific method.

Cut-off levels and detection limits have not been established for the ring-substituted amfetamines. However, some cross-reactivity data have been reported and these data can be compared to cross-reactivities and cut-off levels for amfetamine and methamfetamine to estimate cut off levels of some of the ring-substituted analogues.

Gas Chromatography

MDA has been detected and measured in human plasma and urine samples using gas liquid chromatography with either flame-ionization detection or electron capture detection (Cimbura, 1973; Midha et al., 1976; Midha et al., 1979). Following extraction MDA and MDMA are converted to derivatives such as trifluoroacetates, heptafluorobutyrates or N-pentafluorobenzamides for analysis by gas chromatography. GC with electron capture detection can measure MDA and MDMA levels in the low nanogram range (Midha et al., 1979). Flame ionization detection allows levels of 0.125 ug of MDA from plasma to be determined with a precision of $\pm$ 3.16%.

Spectroscopy

Cimbura (1973) and Lukaszewski (1979) used ultraviolet (UV) spectroscopy to measure MDA levels in urine, blood, bile, stomach contents and liver tissue from overdose victims.

Spectrometry

Gas chromatography/mass spectrometry (GC/MS) has been used to confirm the presence of MDA and MDMA in plasma, urine, bile and liver (Lukaszewski, 1979; Midha et al., 1976; Midha et al., 1979; Fitzgerald et al., 1989). Following extraction, both drugs were converted to such derivatives as trifluoroacetates, isothiocyanates, heptafluorobutyrates or N-pentafluorobenzamides for analysis by GC/MS.

Mass spectrometry has been used to examine the metabolism of MDMA in rats. Yousif et al. (1990), using high pressure liquid chromatography in conjunction with GC/MS identified the MDMA metabolites, MDA and N-methyl-1-(4-hydroxy-3-methoxyphenyl)-2-aminopropane in rat urine. Cho et al. (1990) used capillary gas chromatography linked to mass spectroscopy to identify MDA in the plasma of rats previously injected intravenously with MDMA.

Lim and Foltz (1989) recently reported the detection of MDMA and a number of MDMA metabolites in a urine sample from a fatally injured motorcyclist known to have ingested MDMA. Following extraction from urine and derivatization with trifluoroacetate, metabolites were analyzed by capillary gas chromatography/mass spectrometry under both electron impact and positive ion chemical ionization. Metabolites detected included 3-hydroxy-4-methoxymethamfetamine, 4-hydroxy-3-methoxymethamfetamine, 4-hydroxy-3-methoxyamfetamine, 3,4-dihydroxymethamfetamine and 3,4-(methylenedioxy)phenylacetone.

Solid Dosage Forms

Melting Point Determinations

The melting points for the HCl forms of MDA, MDMA, MDE and N-OH-MDA were obtained from Braun et al. (1980). Shulgin and Carter (1975) determined the melting point of 2-CB HCl. The melting points of the PMMA HCl and N,N-DMA HCl were acquired from NIDA (1988).

Colour Tests

Various colour tests used can be found in the United Nations Manual, ST/NAR/12-13 (1988).

Additional References: Churchill, 1985; Gaston and Rasmussen, 1972; Roverman, 1986.

Chromatography

Thin-Layer Chromatography

Descriptions of the test conditions used in the four thin-layer chromatographic systems are provided below.

System A: Methanol : concentrated ammonia (100:1.5), Silica gel GF. After thorough drying visualization was done with ninhydrin or/and fast black K reagents. (United Nations Manual, ST/NAR/12, 1988).

System B: Ethyl acetate : methanol : concentrated ammonia (85:10:5), silical gel G. After thorough drying visualization was performed with ninhydrin or/and fast black K reagents. (United Nations Manual, ST/NAR/12, 1988).

System C: Chloroform : methanol : concentrated ammonia (90:10:1), Silica Gel G. Visualization with iodine. (NIDA, 1988)

System D: Chloroform : methanol : concentrated ammonia (80:18:2), Silica Gel G. Visualization with iodine. (NIDA, 1988)

Additional References: Churchill, 1985; Koverman, 1986.

Gas-Chromatography

Gas chromatographic (GC) data were obtained from the United Nations Manual (1988). Experimental conditions of the packed column technique and the capillary column technique are given below.

Packed Column Technique

Column. Glass column of 2 m length and 2 mm I.D. packed with 3% OV-17 on Supelcoport or 3% SE-30 or OV-1 on Supelcoport or Chromosorb W-HP.
Column Temperature. Programmed from 130 °C to 260 °C at 16 °C/minute.
Carrier Gas. Nitrogen at a flow rate of 30 ml/minute.
Internal Standard. n-Tetradecane or other n-alkanes.
Detector. Flame Ionization Detector
Injector/Detector Temperature. 280 °C.

Capillary Column Technique

Column. Fused silica length 50 m, I.D. 0.32 mm, coated with Ultra 2 Crosslinked 5% Phenyl methyl silicone at a film thickness of 0.52 um.
Column Temperature. Programmed from 150 °C to 280 °C at 5 °C/minute with a hold of 2 minutes.
Injector Temperature. 250 °C.
Carrier Gas. Nitrogen flow rate of 40 cm/sec.
Internal Standard. n-Tetradecane or other n-alkanes
Detector. Flame Ionization Detector
Detector Temperature. 280 °C.
Split Ratio. 40:1

Note that N-hydroxy-3,4-methylenedioxyamfetamine undergoes pyrolytic disproportionation to yield MDA and an oxime under gas chromatographic analysis conditions and must therefore be analyzed as a derivative (Braun et al., 1980; Dal Cason, 1987; Noggle et al., 1988). In this context, with the exception of N,N-dimethylamfetamine, the substances dealt with under this chapter can also be analyzed as derivatives (Wallace et al., 1977; Rafla and Epstein, 1979; Verebey and De Pace, 1989).

Additional References: Gaston and Rasmussen, 1972.

High Performance Liquid Chromatography.

High performance liquid chromatography (HPLC) data were obtained from the United Nations Manual (1988). Conditions for normal phase and reverse phase chromatography are given below.

Normal Phase

Column. 125 mm by 4.9 mm I.D. stainless steel, packed with Silica HPLC grade, 5 um diameter (Spherisorb S5W or equivalent).
Mobile Phase. Methanol:aqueous ammonium nitrate buffer solution (90:10 v/v). To prepare buffer solution add 94 ml of concentrated ammonia and 21.5 ml concentrated nitric acid to 884 ml water and then adjust the pH to 10 with ammonia.
Flow Rate. 2.0 ml per minute.
Internal Standard. Phenethylamine or other analogue.
Detector. Ultraviolet at 254 nm.

Reversed-Phase

Column. 250 mm by 4 mm I.D. stainless steel, packed with octadecyl-silica HPLC, 5 um diameter (Lichrosorb RP-18 or equivalent)
Mobile Phase. Acetonitrile:1% aqueous ammonium acetate:2.5%aqueous diethylamine (40:45:15). The pH is adjusted to 8-9 by additon of ammonia or acetic acid.
Flow Rate. 1.5 ml per minute
Temperature. 35 °C
Internal Standard. Phenethylamine or other analogue
Detector. Ultraviolet at 254 nm.

Note: These substances, with the exception of N,N-dimethylamfetamine can also be analyzed under reversed-phase conditions as derivatives (United Nations Document, 1990).

Additional References: Peek and Wells, 1986; Noggle et al., 1986; Noggle et al., 1988.

Spectroscopy/Spectrometry

Ultraviolet Spectroscopy.

Spectral data were obtained by dissolving an appropriate amount of the substances under consideration in the desired solvent and by recording transmittance over a wavelength range from 220 to 340 nm. Data is presented as wavelengths of maximum absorbance. Ultraviolet spectral data for 2-CB and PMMA were obtained from Ragan et al. (1985) and Bailey et al. (1973), respectively. The ultraviolet spectral data of N,N-DMA was obtained from Alvarez and Goldston (1979). Ultraviolet spectral data for MDA, MDMA, MDE and N-OH-MDA were obtained from the United Nations Narcotic Laboratory in Vienna, Austria.

Additional References: Gaston and Rasmussen, 1972; Koverman, 1986; Churchill, 1985; Tackett et al., 1988.

Infrared Spectroscopy.

Spectra of the bases were recorded on neat thin film KBr disks. Spectra of the hydrochlorides were recorded on KBr disks obtained by mixing an appropriate amount of the hydrochloride to potassium bromide. The infrared spectra of DL-N-OH-MDA HCl, N,N-DMA HCl and 2-CB were obtained from DEA Special Testing and Research Laboratory. The infrared spectrum of MDE HCl was obtained from Mills and Roberson, 1987. The infrared spectra of MDA HCl and MDMA HCl were obtained from the United Nations Manual (1988). The infrared spectrum of PMMA was obtained from Analytical Profiles of Amphetamines and Related Phenethylamines published by CND Analytical Inc.

Additional References: Churchill, 1985; Noggle et al., 1986; Koverman, 1986; Vallejo, 1982; Hugel and Weaver, 1988; Dal Cason, 1987; Noggle et al., 1988. Tackett et al., 1988.

Mass Spectrometry

Mass spectra were recorded under electron ionization at 70 eV. The mass spectra of N,N-DMA, PMMA and 2-CB were acquired from the DEA Special Testing and Research Laboratory. Mass spectra of MDA, MDMA and MDE were acquired from Mills and Roberson (1987). The mass spectrum of N-OH-MDA was obtained from Noggle et al. (1988).

Additional References: Gaston and Rasmussen, 1972; Vallejo, 1982; Churchill, 1985; Dal Cason, 1987; Hugel and Weaver, 1988; Noggle et al., 1988; Tackett et al., 1988.

3,4-METHYLENEDIOXYAMFETAMINE

CAS Registry Number: 4764-17-4

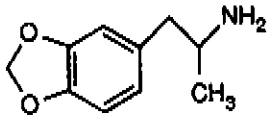
IUPAC Name: a-Methyl-3,4-(methylenedioxy)phenethylamine

CA Index Name: a-Methyl-1,3-benzodioxole-5-ethanamine

Other Names: 3,4-Methylenedioxyphenylisopropylamine
1-(3,4-Methylenedioxyphenyl)-2-aminopropane
3,4-Methylenedioxy-a-methyl-benzeneethanamine
3,4-(Methylenedioxy)amfetamine
Tenamfetamine; Tenanfetamine; SKF-5; MDA

International Control: I, 1971 Convention

Chemical Structure:



M.F.: $C_{10}H_{13}NO_2$ **M.W.:** 179.2
$C_{10}H_{14}ClNO_2$ (HCl) 215.7 (HCl)

Physical Appearance. Base is a colourless oil. HCl is a white powder.

Chemical/Physical Properties.

M.P.: 187-188 °C (HCl)

Solubility: Base is soluble in ethanol, diethyl ether, chloroform and other organic solvents. HCl is soluble in ethanol, water and slightly soluble in chloroform.

Stereochemistry: 2 Enantiomers and 1 racemate.

Colour Tests. Marquis - dark blue --> black
Mecke - green --> dark blue
Gallic Acid - dark green

Thin-Layer Chromatography. System A - Rf 0.39; System B - Rf 0.53; System C - Rf 0.37; System D - Rf 0.67.

Gas Chromatography.

Packed Column - without derivatization: RT 4.77 min.
- with derivatization: RT 8.01 min.

Capillary Column - without derivatization: RT 11.00 min.
- with derivatization: RT 19.00 min.

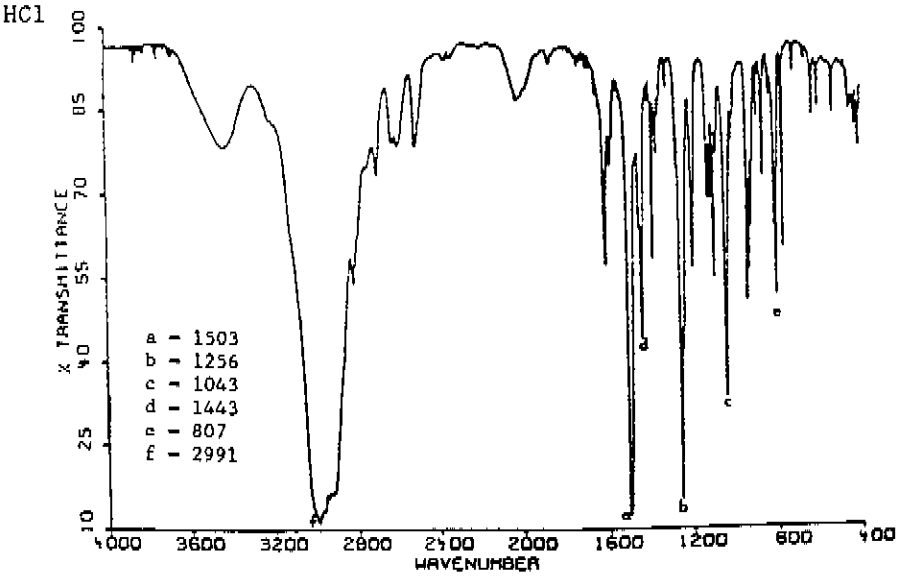
High-Performance Liquid Chromatography

Normal-Phase - RT 2.02 min.
Reversed-Phase - RT 6.63 min.

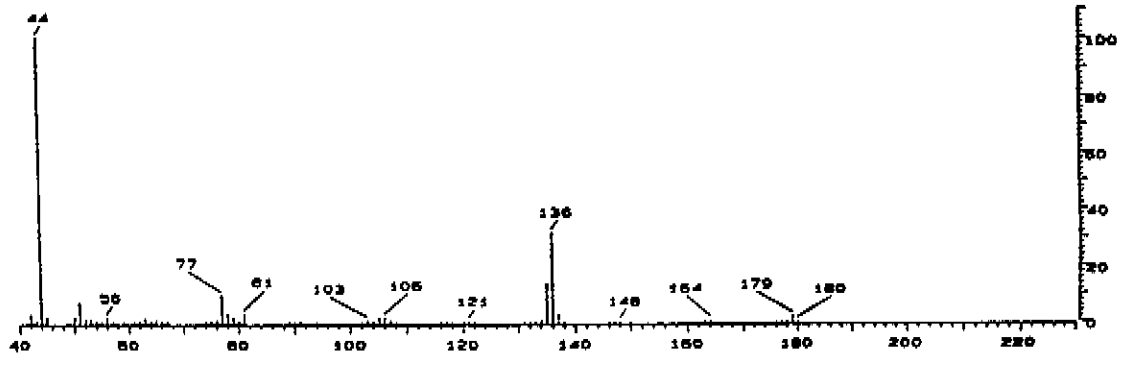
Ultraviolet Spectroscopy

Acidic Solution - 233.8 nm, 285 nm.
Alkaline Solution - 232.4 nm, 285.2 nm.
Neutral Solution - 236.4 nm, 286.8 nm.

Infrared Spectrum.



Mass Spectrum.



3,4-METHYLENEDIOXYMETHAMFETAMINE

CAS Registry Number: 42542-10-9

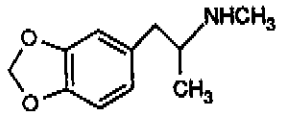
IUPAC Name: N,a-Dimethyl-3,4-(methylenedioxy)phenethylamine

CA Index Name: N-a-Dimethyl-1,3-benzodioxole-5-ethanamine

Other Names: N-Methyl-3,4-methylenedioxy-a-methylbenzeneethanamine
5-(N,a-Dimethyl)ethanamine-1,3-benzodioxole
N-Methyl-3,4-methylenedioxyamfetamine
1-(3,4-Methylenedioxyphenyl)-N-methyl-aminopropane
Methylenedioxymethamfetamine
MDMA; MDM; Ecstasy; XTC; ADAM; ESSENCE

International Control: I, 1971 Convention

Chemical Structure:



M.F.: $C_{11}H_{15}NO_2$ — **M.W.:** 193.2
$C_{11}H_{16}ClNO_2$ (HCl) — 229.7 (HCl)

Physical Appearance: Base is a colourless oil. HCl is a white solid.

Chemical/Physical Properties.

M.P.: 152-153 °C (HCl)

Solubility: Base is soluble in ethanol, diethyl ether, chloroform and other organic solvents. HCl is soluble in ethanol, water and slightly soluble in chloroform.

Stereochemistry: 2 Enantiomers and 1 racemate.

Colour Tests. Marquis - dark blue
Simon - blue
Mecke - green --> dark blue
Gallic Acid - dark green

Thin-Layer Chromatography. System A - Rf 0.29; System B - Rf 0.48; System C - Rf 0.34; System D - Rf 0.64.

Gas Chromatography.

Packed Column - without derivatization: RT 5.02 min.
- with derivatization: RT 8.53 min.

Capillary Column - without derivatization: RT 12.01 min.
- with derivatization: RT 20.85 min.

High-Performance Liquid Chromatography

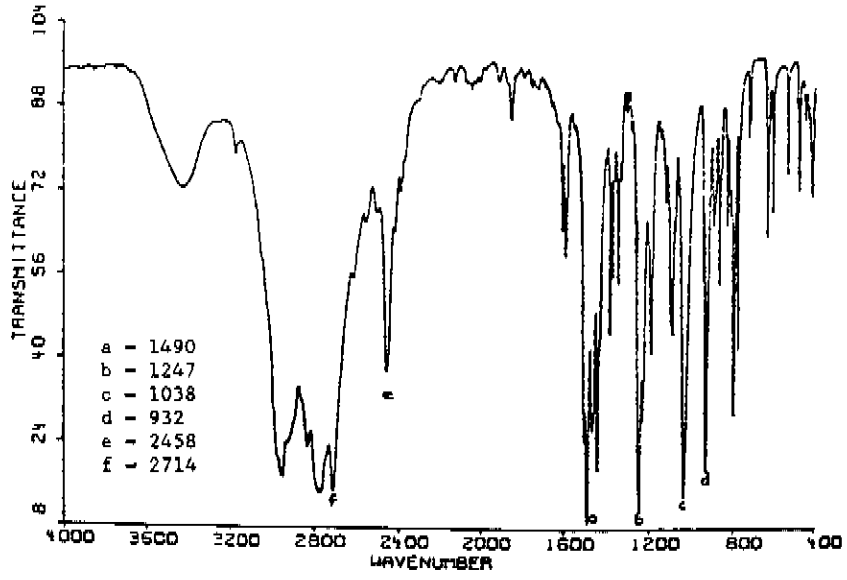
Normal-Phase - RT 3.09 min.
Reversed-Phase - RT 12.70 min.

Ultraviolet Spectroscopy

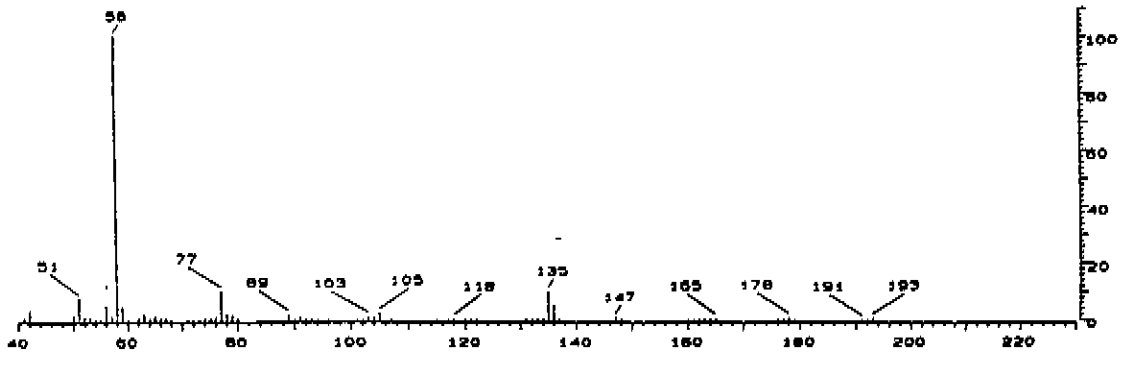
Acidic Solution - 234.2 nm, 285 nm.
Alkaline Solution - 232.6 nm, 285.4 nm.
Neutral Solution - 236.2 nm, 287 nm.

Infrared Spectrum.

HCl



Mass Spectrum.



N-ETHYL-3,4-METHYLENEDIOXYAMFETAMINE

CAS Registry Numbers: 14089-52-2 (Base); 74341-78-9 (HCl)

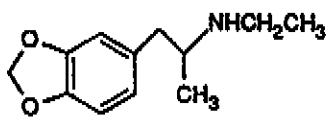
IUPAC Name: N-Ethyl-a-methyl-3,4-(methylenedioxy)phenethylamine

CA Index Name: N-Ethyl-a-methyl-1,3-benzodioxole-5-ethanamine

Other Names: 3,4-Methylenedioxy-N-ethylamfetamine
3,4-Methylenedioxyethamfetamine
3,4-Methylenedioxyethylamfetamine
N-Ethyltenamfetamine
N-Ethyl-3,4-methylenedioxyamfetamine
N-Ethyl-3,4-methylenedioxyphenylisopropylamine
1-(3,4-Methylenedioxyphenyl)-2-ethylaminopropane
MDEA; MDE; Eve

International Control: I, 1971 Convention

Chemical Structure:



M.F.: $C_{12}H_{17}NO_2$ **M.W.:** 207.27
$C_{12}H_{18}ClNO_2$ (HCl) 243.74(HCl)

Physical Appearance: Base is a viscous colourless oil. HCl consists of fine white needles.

Chemical/Physical Properties.

M.P.: 201-202 °C (HCl)

Solubility: Base is soluble in ethanol, diethyl ether, chloroform and other organic solvents. HCl is soluble in ethanol, water and slightly soluble in chloroform.

Stereochemistry: 2 Enantiomers and 1 racemate

Colour Tests. Marquis - dark blue --> black
Simon - blue
Mecke - green --> dark blue
Gallic Acid - dark green --> brown

Thin-Layer Chromatography. System A - Rf 0.44; System B - Rf 0.68; System C - Rf 0.45; System D - Rf 0.74.

Gas Chromatography.

Packed Column - without derivatization: RT 5.29 min.
- with derivatization: RT 8.71 min.

Capillary Column - without derivatization: RT 12.94 min.
- with derivatization: RT 21.68 min.

High-Performance Liquid Chromatography.

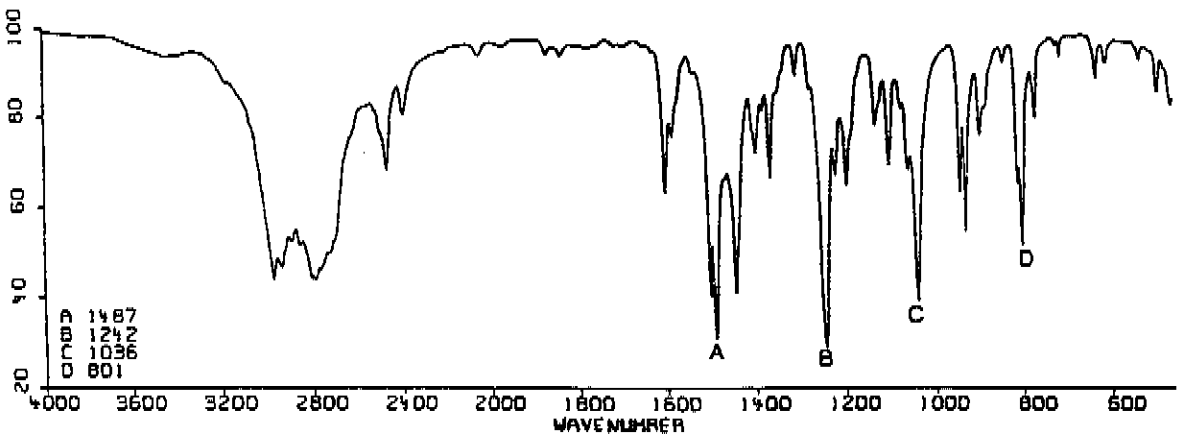
Normal-Phase - RT 2.20 min.
Reversed-Phase - RT 11.32 min.

Ultraviolet Spectroscopy.

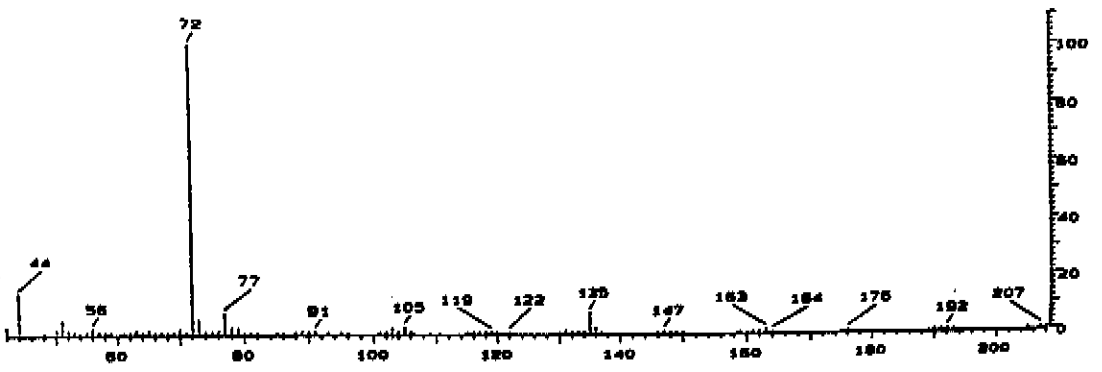
Acidic Solution - 234.2 nm, 285.2 nm.
Alkaline Solution - 233 nm, 285.4 nm.
Neutral Solution - 236 nm, 287.2 nm.

Infrared Spectrum.

HCl



Mass Spectrum.



N-HYDROXY-3,4-METHYLENEDIOXYAMFETAMINE

CAS Registry Number: 74698-47-8 (Base); 74341-83-6 (HCl)

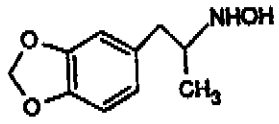
IUPAC Name: N-[a-Methyl-3,4-(methylenedioxy)phenethyl]hydroxylamine

CA Index Name: N-Hydroxy-a-methyl-1,3-benzodioxole-5-ethanamine

Other Names: 3,4-Methylenedioxy-N-hydroxyamfetamine
N-Hydroxy-3,4-methylenedioxyamfetamine
N-Hydroxytenamfetamine
N-Hydroxy-3,4-methylenedioxyphenylisopropylamine
1-(3,4-Methylenedioxyphenyl)-2-hydroxyaminopropane
N-Hydroxy-a-methyl-3,4-(methylenedioxy)phenethylamine
N-Hydroxy-MDA
N-OH-MDA

International Control: I, 1971 Convention

Chemical Structure:



M.F.: $C_{10}H_{13}NO_3$ M.W.: 195.22
$C_{10}H_{14}ClNO_3$ (HCl) 231.68 (HCl)

Physical Appearance: Base is a white solid. HCl is a white crystalline powder.

Chemical/Physical Properties.

M.P.: 149-150 °C (HCl)

Solubility: Base is soluble in methylene chloride and slightly soluble in isopropyl alcohol. It is also soluble in ethanol, diethyl ether, chloroform and other organic solvents. HCl is soluble in ethanol and water and slightly soluble in chloroform.

Stereochemistry: 2 Enantiomers and 1 racemate.

Colour Tests. Marquis - dark blue --> black
Mecke - green --> dark blue --> black
Gallic Acid - dark green --> brown

Thin-Layer Chromatography. System A - Rf 0.84; System B - Rf 0.76; System C - Rf 0.54; System D - Rf 0.75.

Gas Chromatography.

Packed Column - with derivatization: RT 9.35 min.
Capillary Column - with derivatization: RT 22.66 min.

High Performance Liquid Chromatography

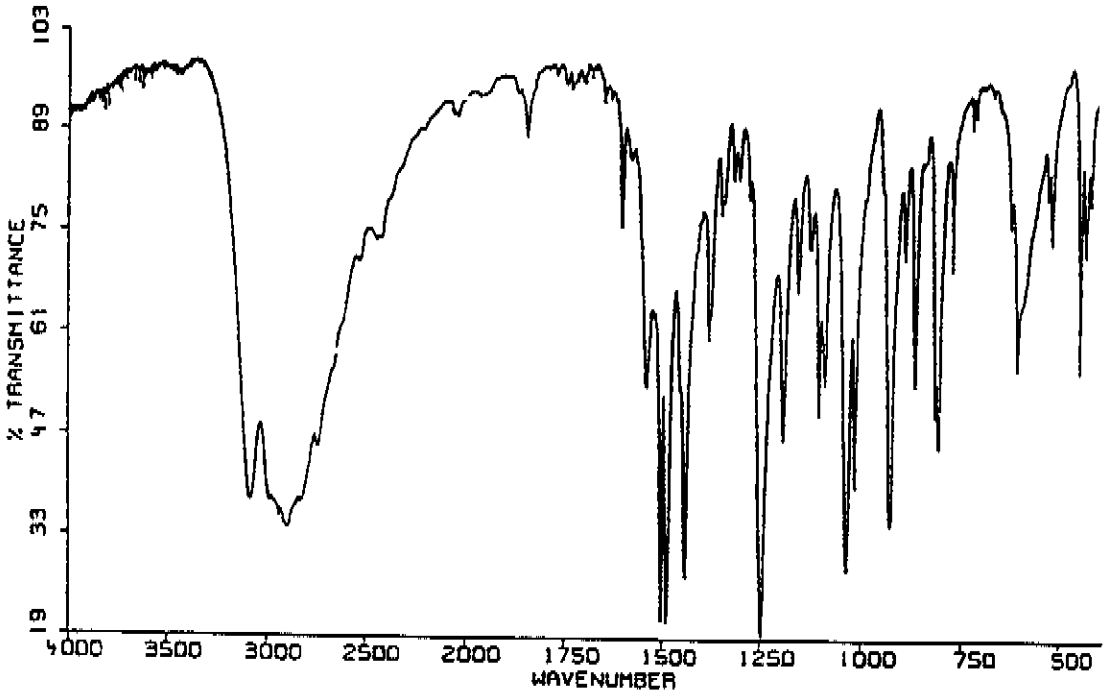
Normal-Phase - RT 1.23 min.
Reversed-Phase - RT 4.56 min.

Ultraviolet Spectroscopy

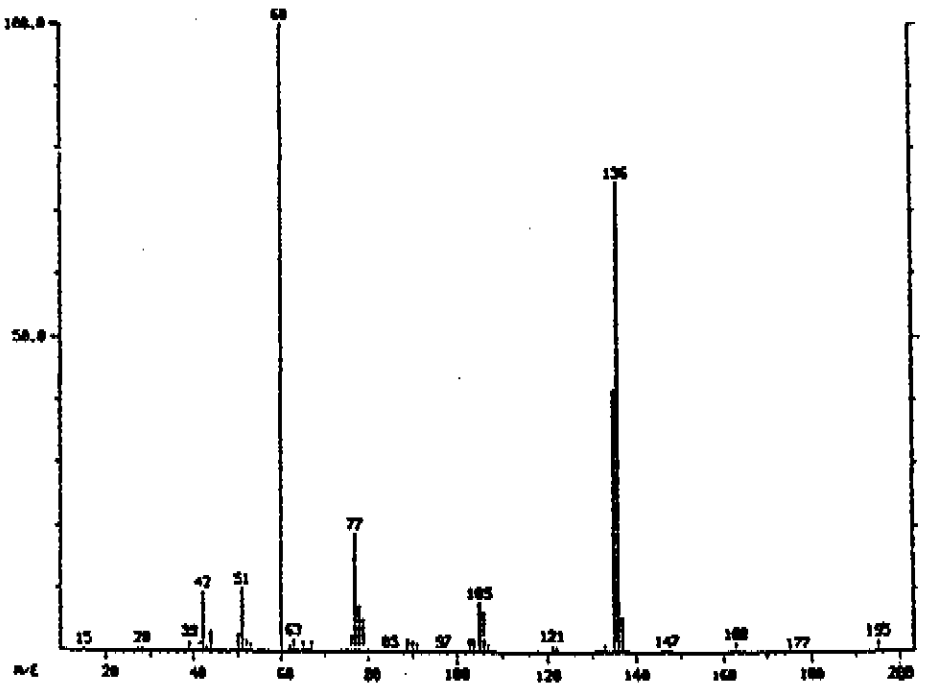
Acidic Solution - 234.2 nm, 285.2 nm.
Alkaline Solution - 219.6 nm, 285.4 nm.
Neutral Solution - 234.6 nm, 287 nm.

Infrared Spectrum.

dl-N-OH-MDA HCl



Mass Spectrum.



4-METHOXYMETHAMFETAMINE

CAS Registry Number: 22331-70-0

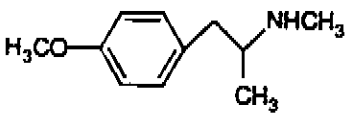
IUPAC Name: p-Methoxy-N,a-dimethylphenethylamine

CA Index Name: 4-Methoxy-N,a-dimethylbenzeneethanamine

Other Names: 1-(4-Methoxyphenyl)-2-methylaminopropane
(4-Methoxyphenyl)isopropylmethylamine
4-Methoxy-N,a-dimethylphenethylamine
4-Methoxy-N-methylamfetamine
N,a-Dimethyl-p-methoxy-phenethylamine
N,a-Dimethyl-4-methoxy-phenethylamine
N,a-Dimethyl-p-methoxypropanamine
Para-Methoxymethamfetamine
PMMA

International Control: Not Controlled.

Chemical Structure:



M.F.: $C_{11}H_{17}NO$ **M.W.:** 179.3
$C_{11}H_{18}ClNO$ (HCl) 215.8 (HCl)

Physical Appearance: HCl is a white solid.

Chemical/Physical Properties.

M.P.: 177-179 °C (HCl)

Solubility: Base is soluble in ethanol, diethyl ether, chloroform and other organic solvents. HCl is soluble in ethanol and water and slightly soluble in chloroform.

Stereochemistry: 2 Enantiomers and 1 racemate

Colour Tests. Mecke - yellow --> yellow orange

Thin-Layer Chromatography. System C - Rf 0.31

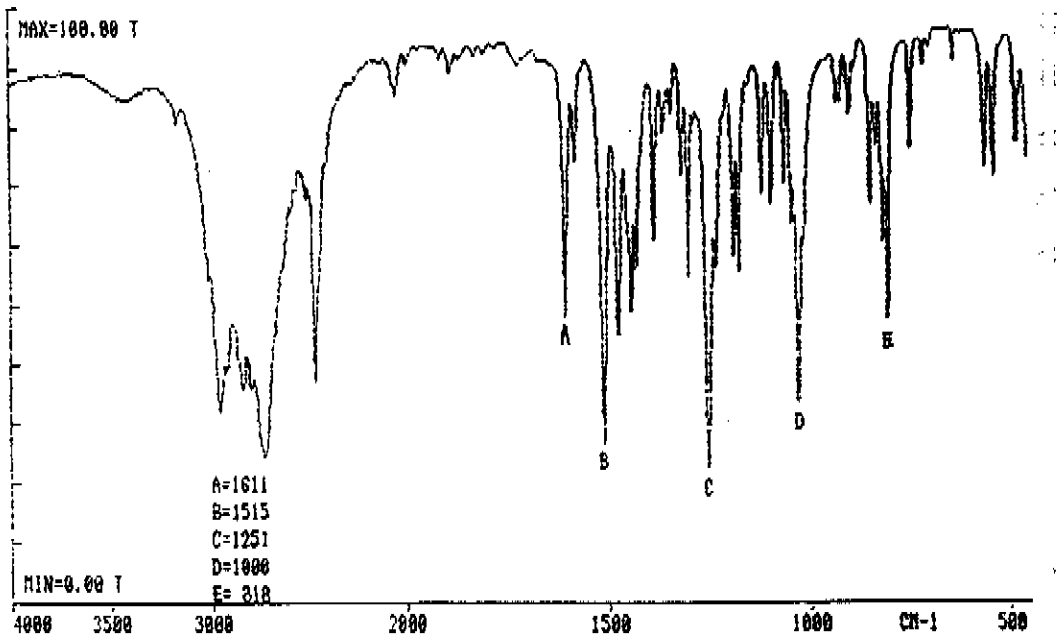
Gas Chromatography.

Capillary Column - without derivatization: RT 5.84 min.

Ultraviolet Spectroscopy.

Neutral Solution - 276 nm, 282 nm.

Infrared Spectrum.
HCl



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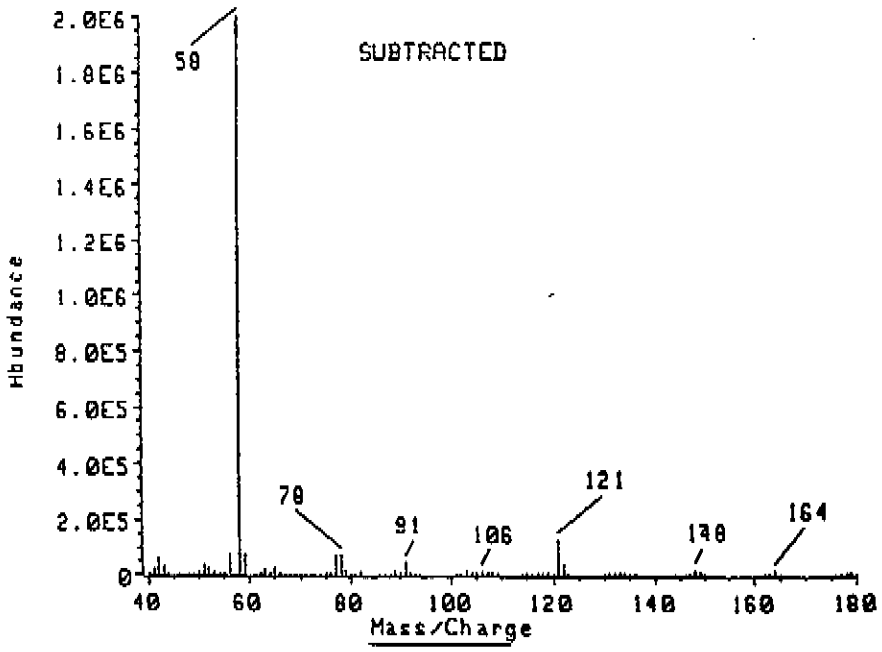
Mass Spectrum.



4-BROMO-2,5-DIMETHOXYPHENETHYLAMINE

CAS Registry Number: 66142-81-2

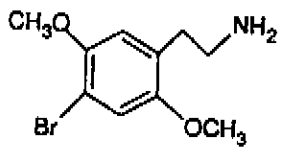
IUPAC Name: 4-Bromo-2,5-dimethoxyphenethylamine

CA Index Name: 4-Bromo-2,5-dimethoxybenzeneethanamine

Other Names: 2-CB; BDMPEA; MFT

International Control: Not Controlled.

Chemical Structure:



M.F.: $C_{10}H_{14}BrNO_2$ **M.W.:** 260.1
$C_{10}H_{15}BrClNO_2$ (HCl) 296.6 (HCl)

Physical Appearance: HCl is a white solid.

Chemical/Physical Properties:

M.P.: 237-239 °C (HCl)

Solubility: Base is soluble in ethanol, diethyl ether, chloroform and organic solvents. HCl is soluble in ethanol and water and slightly soluble in chloroform.

Colour Tests. Marquis - orange --> brown
Mecke - green --> yellow --> blue

Thin-Layer Chromatography. System D - Rf 0.58

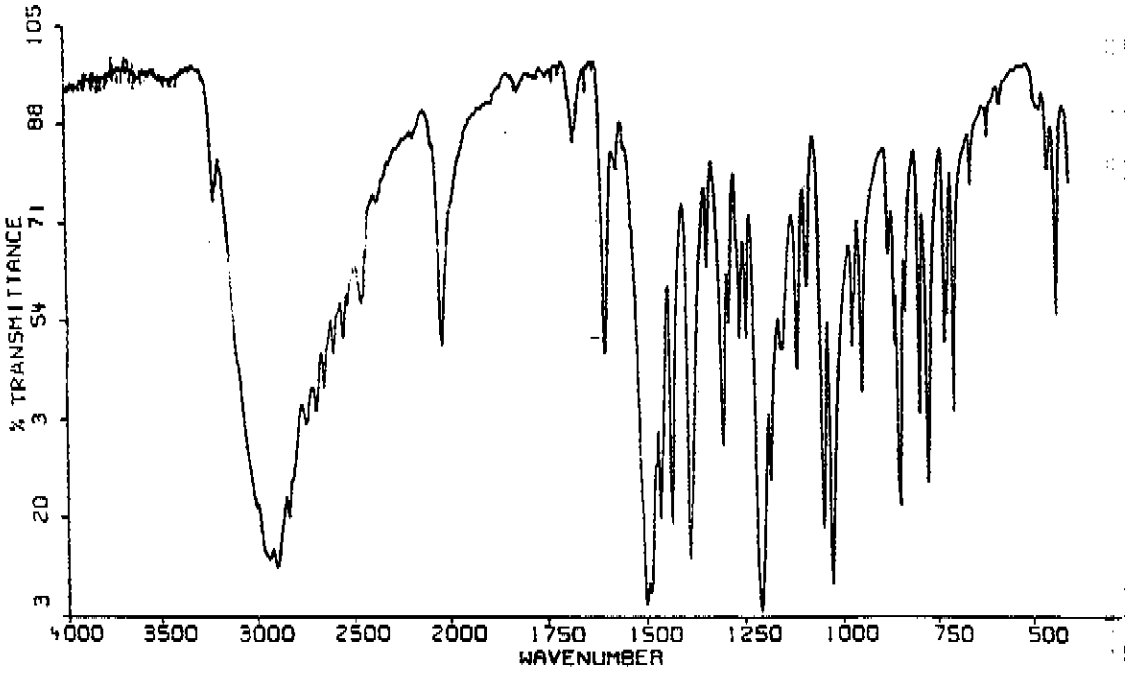
Gas Chromatography.

Packed Column - without derivatization: Rt 6.10 min.

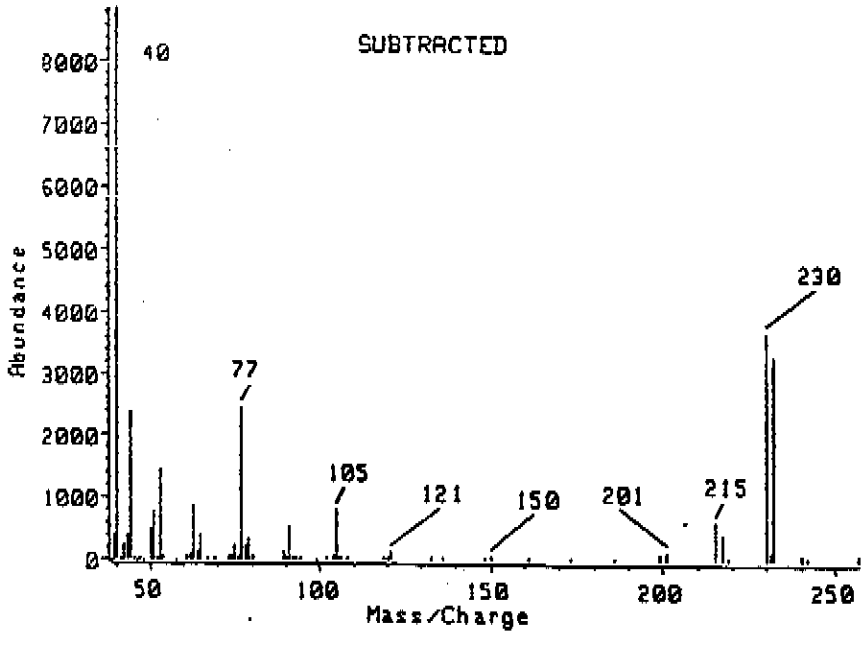
Ultraviolet Spectroscopy.

Acidic Solution - 256 nm, 294 nm.

Infrared Spectrum.
HCl.



Mass Spectrum.



N,N-DIMETHYLAMFETAMINE

CAS Registry Number: 4075-96-1

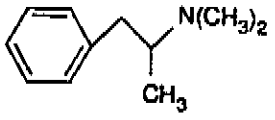
IUPAC Name: N,N,a-Trimethylphenethylamine

CA Index Name: N,N,a-Trimethylbenzeneethanamine

Other Names: N,N-Dimethyl-a-methyl-benzeneethanamine
N,N-Dimethyl-a-methyl-phenethylamine
N,N-a-Trimethyl-benzenethanamine
1-Phenyl-2-dimethylaminopropane
(Phenylisopropyl)dimethylamine
Dimetamfetamine
Dimephenopan
Dimephenopane
Dimethamfetamine
Dimethylpropamine
Dimethylamphetamine
Metromin
Metrotonin
N,N-DMA

International Control: Not Controlled.

Chemical Structure.



M.F.: $C_{11}H_{17}N$
$C_{11}H_{18}ClN$ (HCl)

M.W.: 163.3
199.7 (HCl)

Physical Appearance: HCl is a white solid.

Chemical/Physical Properties.

M.P.: 181-183 °C (HCl)

Solubility: Base is soluble in ethanol, diethyl ether, chloroform and organic solvents. HCl is soluble in ethanol and water and slightly soluble in chloroform.

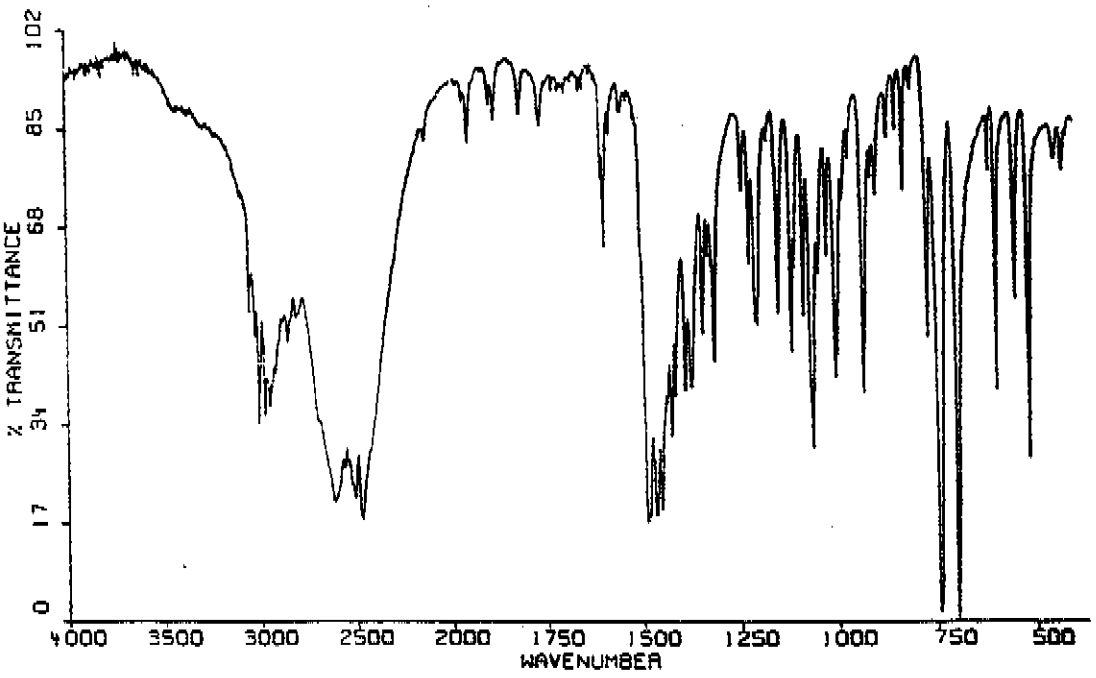
Stereochemistry: 2 Enantiomers and 1 racemate.

Thin-Layer Chromatography. System D - Rf 0.74

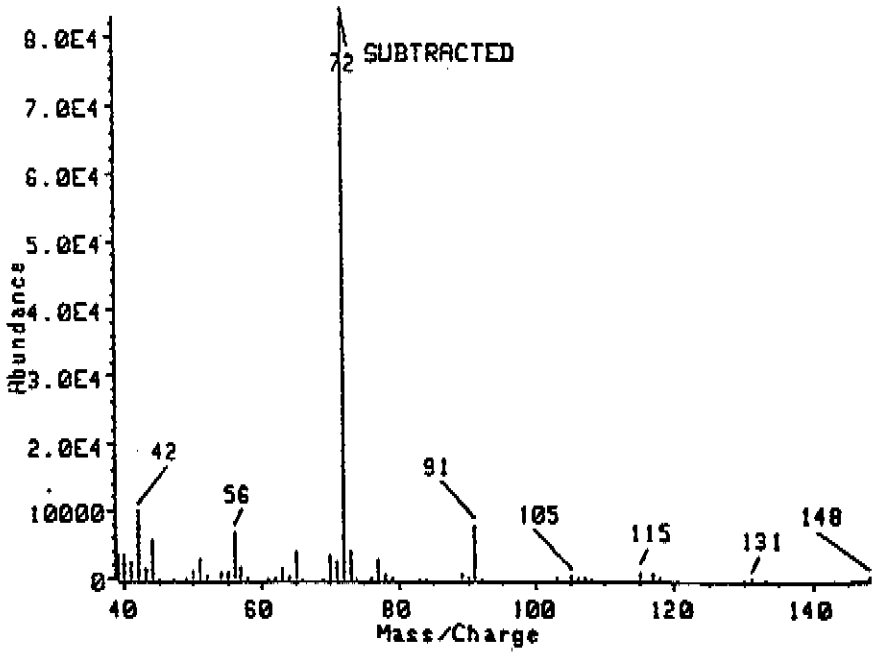
Ultraviolet Spectroscopy.

Acidic Solution - 251 nm, 257 nm, 263 nm
Alkaline Solution - 258 nm, 268 nm

Infrared Spectrum.
d-HCl



Mass Spectrum.



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PHENCYCLIDINE ANALOGUES

GENERAL STATEMENT OF THE PROBLEM

A number of phencyclidine (PCP) analogues have appeared in the illicit drug traffic in the United States. These analogues include N-ethyl-1-phenylcyclohexylamine (PCE), 1-(1-(2-thienyl)cyclohexyl)piperidine (TCP), 1-(1-phenylcyclohexyl)pyrrolidine (PCPy) and 1-(1-(2-thienyl)cyclohexyl)pyrrolidine (TCPy). Like phencyclidine, the parent compound, they are readily synthesized in clandestine laboratories from readily available chemicals using simple laboratory techniques. A limited number of studies have provided evidence that these analogues produce psychotomimetic effects and other pharmacological effects similar to those produced by PCP. The psychotomimetic effects of PCP cause changes in behavior which pose a health threat to the user and to individuals associated with the user. Although PCP and its analogues have been synthesized, distributed and abused primarily in the U.S., their powerful psychotomimetic effects and ease of clandestine synthesis make them a serious health threat worldwide.

GENERAL HISTORY

Legitimate Use

PCP was synthesized and developed as a general anesthetic for use in humans in the latter half of the 1950s by the Parke Davis Co. in the U.S. It was first marketed under the trade name Sernyl. PCP produced excellent surgical anesthesia without respiratory or cardiovascular depression. Unfortunately, by 1959 evidence had accumulated to indicate that a small percentage (10 to 20%) of patients emerging from anesthesia induced by PCP experienced delirium and hallucinogenic-like effects. The occurrence of these effects resulted in PCP being removed from the U.S. market in 1965. In the early 1960s various laboratory studies showed that PCP was an effective anesthetic and immobilizing agent for various animals. In 1967 PCP was first marketed in the U.S. under the tradename, Sernylan, as a veterinary anesthetic, particularly for primates. Use of Sernylan was discontinued in 1979.

In the early 1960s Parke Davis Co. synthesized and patented a number of PCP analogues including PCE, PCPy and TCP. Parke Davis attempted to develop PCE and TCP as adjuncts to surgical anesthesia but eventually abandoned the idea. To date none of the PCP analogues have been used for legitimate medical purposes.

Illicit Use

PCP first appeared in the illicit drug market in California in 1967. At that time PCP was primarily distributed as capsules or tablets under such street names as "Peace Pill" and "Hog." Frequent use of high doses resulted in a proliferation of reports of unpleasant experiences associated with the use of PCP. These reports lead to a transient decline in the popularity of PCP use. Within several years, however, PCP was again on the street initially being sold as other drugs (i.e. LSD, THC, mescaline) or as an adulterant of other drugs. Abusers started mixing PCP powder and crystals (street name "angel dust") with various leafy materials (i.e. marijuana, tobacco, parsley and mint leaves) which were subsequently smoked. In the early 1970s PCP use spread rapidly into many U.S. urban centers. PCP abuse in the U.S. peaked in the middle to late 1970s and

early 1980s. Over the last few year PCP use has declined to relatively low levels.

A number of PCP analogues have been identified in the illicit drug traffic in the U.S. PCE was first identified in 1969 in California. This potent analogue of PCP was available as a brown, purple, pink or off-white powder or tablet. It was sold as PCP under the street name "Rocket Fuel." TCP and PCPy were first identified in the early 1970s. Both analogues were widely distributed as PCP in powder or tablet form during the 1970s. Beginning around 1981 the use of PCE, TCP and PCPy started to decline rapidly. Since approximately 1984, these analogues have seldom been detected in the illicit drug traffic in the U.S. In 1988 TCPy was briefly detected in powdered samples sold as PCP.

PHARMACOLOGY

General Effects

A number of reports have described the pharmacological effects of psychoactive doses of PCP in human volunteers and surgical patients. At single, low intravenous doses of 0.075 to 0.1 mg/kg PCP causes estrangement, thought disorganization, perceived changes in body image, negativism, drowsiness, apathy and feelings of inebriation. At higher doses effects include analgesia, dizziness, strange and unusual physical sensations, and thought disorganization. Concentration, learning and memory are impaired. At the highest doses (1 mg/kg), anesthesia with catatonia and muscle rigidity is observed. Following emergence from anesthesia, a small percentage of individuals experience a reemergence syndrome consisting of agitation, violent reactions, convulsions, diplopia, dizziness and nystagmus.

A limited number of clinical studies have shown that TCP and PCE produce effects similar to those of PCP. At low doses these analogues produce a generalized numbness, sensations characterized as "going away" or "drifting" and general inebriation. At sufficiently high doses analgesia and anesthesia associated with catatonia and generalized rigidity occur. Following emergence from anesthesia, some individuals display pronounced adverse effects such as agitation, violent behavior or hallucinations.

In laboratory animals PCP and its analogues produce a wide range of pharmacological effects including anticonvulsant effects, analgesia, catatonia, anesthesia and ataxia. The exact mechanisms whereby PCP produces these effects and the psychotomimetic effects observed in humans are not known. Animal studies have shown that PCP alters the function of a variety of transmitter systems including the noradrenergic, serotonergic and cholinergic systems. In addition, PCP alters physiological processes involving gamma-aminobutyric acid and excitatory amino acids. Many of these effects result from the activation of putative PCP receptors. TCP, PCPy, PCE and TCPy also bind to these putative PCP receptors.

Animal studies suggest that PCP and its analogues have a significant abuse liability. Tolerance and physical dependence develop with chronic administration of PCP. PCP, TCP, PCE, PCPy and TCPy have reinforcing properties as indicated by their ability to support self-administration behavior in laboratory animals. TCP, PCE, PCPy and TCPy share discriminative stimulus properties with PCP.

Structure Activity Relationships

Structure activity relationships of PCP-like compounds have been examined in animals, but not humans. These studies have examined the effects of alterations of PCP structure on such effects as rota-rod activity and PCP-like drug discrimination in laboratory animals. These studies show that selected changes in the structure of PCP cause changes in pharmacological activity. Replacing the piperidine ring with an ethylamino group to yield PCE causes a 6 fold increase in potency. Potency is also increased by the replacement of the benzene ring with a 2-thienyl to give TCP. Replacement of the piperidine ring of either PCP or TCP with a pyrrolidine ring to yield PCPy or TCPy reduces potency only slightly from the parent compound. Contraction, expansion or cleavage of the cyclohexane ring causes a dramatic reduction in potency.

Routes of Administration and Dosage Forms

PCP and its analogues have been distributed in a variety of forms including tablets, capsules, gums, liquids and powders. A common dosage form is a powder sprinkled on leafy material (i.e. tobacco, marijuana, parley, mint leaves) intended for smoking. Alternatively the leafy material may be dipped in a liquid PCP solution prior to smoking. Less commonly encountered dosage forms are tablets and capsules which have been reported to contain between 1 and 7 mg of PCP.

PCP and its analogues are administered orally or via inhalation. Due to a more efficient titration of dose the preferred route of administration is inhalation of smoke from burned leafy material containing the drug. This route of administration results in the intake of PCP and inactive, pyrolytic degradation products of PCP such as 1-phenylcyclohexane, piperidine and N-acetylpiperidine. PCP and its analogues are seldom administered intravenously.

Pharmacokinetics

Human pharmacokinetic studies have been performed with PCP, but not with any of the PCP analogues. Considering the close similarity of structure and pharmacological activity between PCP and its analogues, it is likely that they all display somewhat similar pharmacokinetic properties. Due to ethical considerations of experimental design, the pharmacokinetics of PCP has primarily been examined in either volunteers receiving oral or intravenous subthreshold pharmacological doses of PCP or in individuals presenting to the emergency room with PCP-induced intoxication.

PCP is readily absorbed and is widely distributed to peripheral tissues. It is well absorbed by oral, percutaneous, pulmonary or nasal routes. Following oral administration of 1 mg of PCP to human volunteers, oral bioavailability averaged 72% with a range of 50 to 90%. Due to pyrolytic breakdown of PCP into 1-phenylcyclohexane and piperidine, approximately one third of a dose of PCP from a cigarette is available for absorption. Once in the lungs absorption of PCP is nearly complete. Due to high lipid solubility, PCP has a large volume of distribution. Following oral administration of a 1 mg dose the volume of distribution is approximately 6.2 $\pm$ 0.3 liters/kg. Blood/plasma ratios approximate 1 and protein binding is about 65%. The large volume of distribution reflects the extensive loss of PCP from blood into various tissues, particularly those with high lipid content such as the liver and brain. Plasma elimination half-life of PCP has been estimated to range from 7 to 46 hours and, in cases of severe intoxication, 1 to 4 days. The extended half-life observed with

severe poisoning may reflect the prolonged slow release of PCP into the blood from tissue stores.

The major route of metabolism of phencyclidine in humans involves oxidative hydroxylation via the cytochrome P-450 enzyme system. Hydroxylation of the piperidine and cyclohexyl groups yield the predominate urinary metabolites 1-(1-phenylcyclohexyl)-4-hydroxypiperidine and 1-(1-phenyl-4-hydroxycyclohexyl)-piperidine, respectively. The dihydroxy metabolite, 4-(4'-hydroxypiperidine)-4-phenylcyclohexanol is also detectable in human urine. All three hydroxylated metabolites are excreted as conjugates in the urine. 5-(N-(1'-Phenylcyclohexylamino)valeric acid is a minor metabolite found in human urine.

A given dose of PCP is excreted primarily in the urine as conjugated, hydroxylated metabolites. Following intravenous administration of a single 1 mg dose, 30% to 50% of the dose is excreted within 7 days and 77% is excreted within 10 days. Only about 2% of the dose is excreted in the feces. Excretion of PCP is highly dependent on the pH of the urine. Acidification of the urine promotes the excretion of PCP.

TOXICOLOGY

Toxic Clinical Manifestations of Drug Use and Overdose

Clinical Presentation

Individuals with acute low-to-moderate dose PCP intoxication following the smoking or snorting of 5 to 15 mg PCP display major behavioral and physiological disturbances. Symptomatology is often similar to functional psychosis. Visual, auditory and tactile misperceptions are commonly observed. Psychotic reactions may last only a few hours or for as long as 1 to 4 weeks. Various signs of catatonia such as mutism, grimacing, repetitive posturing and rigidity may be present. Mental disorientation is often accompanied by alternating periods of lethargy and fearful agitation. Behavioral abnormalities such as bizarre or obscene acts, violence, agitation, anxiety or euphoria may occur. Observed physiological effects may include tachycardia, tachypnea, hypertension, diaphoresis (sweating), salivation, flushing, lacrimation, vomiting, miosis, nystagmus, ataxia, blurred vision, tremors, muscle weakness, rhabdomyolysis, choreoathetosis and renal failure.

Individuals experiencing acute high dose PCP intoxication following administration of 25 mg or more of PCP usually become comatose and fail to respond to painful stimuli. Coma may occur abruptly or following the sudden onset of violent or bizarre behavior. The duration of coma is usually from 2 to 24 hours and rarely as long as 5 to 7 days. Coma may rarely be associated with respiratory depression and apnea. A decreased deep tendon reflex, convulsions, opisthotonos and arrhythmias may also occasionally be observed concomitantly with coma. Following emergence from coma, fluctuating states of consciousness and behavioral and physiological effects seen in low-to-moderate dose PCP intoxication are usually observed.

Prolonged abuse of PCP is associated primarily with personality changes, not adverse physical effects. With continued use tolerance develops to the effects of PCP, thus resulting in a gradual increase in the amounts of PCP administered. With time individuals tend to display increased irritability, bellicose and antisocial behavior, depressed mood and increased frequency of PCP-induced dysphoric experiences. Memory, judgement and cognitive function may also be

adversely affected during chronic abuse of PCP. Upon abrupt discontinuation of chronic PCP use, a mild withdrawal syndrome is occasionally observed. A withdrawal syndrome has also been reported in the neonates of women chronically abusing PCP while pregnant.

There has been one case report of an overdose involving PCP analogues. An individual presented to the emergency room approximately 3 to 4 hours following the ingestion of an unknown amount of PCPy. The individual displayed toxic signs similar to those caused by toxic doses of PCP including horizontal nystagmus, resting tremor of the upper limbs, agitation, hostility, suspiciousness, panic and thoughts of impending doom. Toxicological analysis failed to find any other substance in the urine. The individual was treated with physostigmine and released 48 hours later.

Blood and Tissue Levels

Concentrations of PCP observed in blood and serum samples from PCP-intoxicated individuals range from <5 ug/liter up to about 0.8 to 1.0 mg/liter. The generally low concentrations of PCP observed in blood during periods of intoxication have been attributed to the high lipid solubility of PCP resulting in rapid distribution of the drug out of the blood and into peripheral tissues. Concentration of PCP in blood has not been observed to correlate with physical findings of PCP intoxication.

In PCP intoxication, levels of PCP in urine range from 0.4 to 18 mg/liter. In comatose individuals urine PCP concentrations may range from 0.2 to 142 mg/liter. Urine concentration of PCP depends heavily on the urine pH, with acidic urine showing the highest levels of PCP. Urinary PCP levels do not appear to correlate with the severity of PCP intoxication.

Forensic Toxicology

Fatalities associated with the use of PCP may be divided into two groups. One group involves fatalities in which PCP intoxication is the primary cause of death. In these cases individuals generally ingest enormous amounts (120 to 200 mg) of PCP either accidentally or for purposes of suicide and subsequently die from the toxic effects of the drug. The second group involves fatalities due to trauma received while under the influence of PCP. Most fatalities associated with PCP fall within this group. Trauma results from bizarre, often agitated or violent, behavior and from alterations in mental judgement induced by PCP. Within this group of fatalities examples of causes of death would include stab wounds, gunshot wounds, automobile accidents, drowning or asphyxiation due to smoke inhalation.

Autopsy Findings

Post-mortem examinations of a total of 16 fatalities, attributed directly to PCP intoxication, have been reported. Collectively, these examinations failed to show any pertinent or unusual findings that would specifically indicate PCP involvement. Findings reported included pulmonary edema, moderately to markedly congested liver and, in one case, anoxic petechial hemorrhages in the lungs. In a separate case, pulmonary embolism was detected in an individual who died while being treated for rhabdomyolysis and renal insufficiency, probably indirect effects of PCP intoxication.

Post-mortem examinations of 2 fatalities purportedly involving PCE have been described. In one victim, with the exception of lung adhesions, no abnormalities of the organs were observed during macroscopic or microscopic examination. In the second fatality, congestion and edema of the lungs were noted. In the two fatalities blood levels of PCE were 1.0 and 3.1 mg/liter.

Blood and Tissue Levels

In fatalities due to lethal intoxication with PCP, blood PCP concentrations have ranged from 0.3 to 25 mg/liter. Blood PCP concentrations of 2.0 mg/liter and above have been reported to be uniformly fatal. In these fatalities high levels of PCP were detected in liver and/or brain tissue. Blood concentrations of PCP in fatalities in which PCP toxicity was not the immediate cause of death have been reported to range from a trace amount to 1 mg/liter.

CLINICAL MANAGEMENT

There are no antidotes for the treatment of overdoses of PCP or its analogues. Treatment of PCP analogue intoxication will be similar to the treatment of PCP intoxication and will involve taking steps for supportive care and for promoting the excretion of the toxic drug. Treatment will differ depending on whether the patient presents with low or high overdose.

Patients suffering low-to-moderate dose PCP-like intoxication are usually brought to the emergency room because of behavioral disturbances. Such patients should be placed in a controlled environment to minimize evoking agitated or violent behavior. Diazepam in divided doses may be administered to keep the patient calm. Ammonium chloride or ascorbic acid should be administered to acidify the urine and thus promote the excretion of PCP. Patients experiencing psychotic episodes should be given haloperidol or chlorpromazine. It may be necessary to administer propranolol and a cholinomimetic agent to treat any sympathomimetic and anticholinergic effects.

Patients suffering high overdose will usually be comatose and unresponsive to deep pain upon arrival in the emergency room. Therapy must initially be directed at maintenance of vital life processes. Orotracheal intubation should be performed to prevent ventilatory inadequacy. If ingestion was fairly recent, gastric lavage with activated charcoal may be beneficial. An intravenous line should be established to administer drugs and monitor cardiac and other vital signs. Seizures should be treated with intravenous diazepam. In the absence of myoglobinuria, ammonium chloride and ascorbic acid administered intravenously and followed by furosemide may improve the clinical symptoms by promoting drug excretion. Rare hypertensive crises may be treated with intravenous propranolol or diazoxide. Hyperthermia may be controlled by ice baths. Once the individual has regained consciousness, diazepam and chlorpromazine or haloperidol should be available to control agitated behavior and psychotic reactions.

CLANDESTINE SYNTHESIS

Synthesis I

Phencyclidine and several of its analogues are prepared by the replacement of the cyano group of the corresponding cycloalkylaminocyclohexanecarbonitrile using a Grignard reagent. The carbonitrile intermediate is prepared from an alkylamine, cyclohexanone, hydrochloric acid and sodium or potassium cyanide.

Variation of the cyclic amine (piperidine, pyrrolidine, morpholine) and/or the Grignard reagent (phenyl- or 2-thienyl magnesium bromide) allows the preparation of several analogues.

Synthesis II

PCE is prepared through the intermediate N-cyclohexylidene ethylamine which is formed by the reaction of ethylamine and cyclohexanone followed by the addition of potassium hydroxide and subsequent distillation. The intermediate is then reacted with phenyllithium to form PCE.

Precursors and Essential Chemicals

Alkylamine such as piperidine or pyrrolidine or ethylamine (I,II)
Cyclohexanone (I,II)
Phenylmagnesium bromide or 2-thienylmagnesium bromide (I)
Phenyllithium (II)
Sodium or potassium cyanide (I)
Hydrochloric acid (I)
Sodium bisulfite (I)

ANALYTICAL CHEMISTRY

Body Fluids

The analysis of PCP and its analogues in body fluids requires sensitive and specific techniques. Due to its relatively high lipid solubility, PCP rapidly distributes from the blood to the peripheral tissues. This rapid distribution results in low concentrations (usually below 100 ng/ml) of PCP detected in blood at the time of PCP intoxication. In addition, the concentrations of PCP in the urine are highly dependent on urine acidity. When the urine is alkaline, low levels of PCP may be measured in urine.

Immunoassay

Radioimmunoassays have been used to measure PCP in blood, urine and saliva (Rosenberg and Vunakis, 1979; Weingarten and Trevias, 1982; McCarren et al., 1984). For the assay, sensitivity ranges from 0.5 to 5 ng/ml PCP. Cross reactivity occurs with TCP and, to a lessor extent with PCPy and the morpholine derivative of PCP. There is no cross reactivity with other drugs of abuse.

Enzyme immunoassay techniques provide a rapid method for the qualitation and quantitation of PCP in serum and urine (Walberg and Gupta, 1982; Walberg et al., 1983; Weingarten and Trevias, 1982). Depending on the particular enzyme immunoassay used, the sensitivity of detection ranges from 5 to 75 ng/ml. For this assay cross reaction with other PCP metabolites and analogues does occur; thus, the presence of PCP analogues would yield a false positive test for PCP in this assay. Suspected analogue administration would have to be verified using GC or GC/MS analysis.

Chromatography

Thin-layer chromatography techniques (Jain et al., 1977; Finkle, 1978) are primarily used for the qualitative analysis of PCP, particularly in urine samples. This method, with a lower detection limit of approximate 0.2 to 1 mg/ml

of sample is relatively less sensitive than other available analytical techniques.

Analytical techniques utilizing gas chromatography with flame ionization detectors (GC-FID) and nitrogen phosphorus detectors (GC-NPD) have been developed to quantitatively analyze PCP in blood, serum, urine, CSF, saliva and various tissues including the brain, liver, kidney, etc. (Gupta et al., 1975; Reynolds, 1976; Bailey and Guba, 1980a,b; Lewellen et al., 1979; Micelli et al., 1981; Woodworth et al., 1984 and Holsztynska and Domino, 1986). The lower level of PCP detection using the GC-FID is approximately 75 to 100 ng per ml of sample, thus making it less sensitive than GC-NPD which has a lower limit of detection around 5 ng/ml or less per sample. GC-NPD may be used to detect and quantitate PCP metabolites and analogues in body fluids and tissues.

Spectrometry

Gas chromatography/mass spectrometry is a confirmatory, analytical technique for the detection and quantitation of PCP in blood, serum, urine, CSF, saliva, and various tissues including brain, liver, kidney, etc. (Lin et al., 1975; McLeod et al., 1976; Wong and Biemann, 1976). In general, this technique has a sensitivity ranging from 0.1 to 5 ng/ml of PCP in original sample. Mass spectrometry allows one to make structural determinations of PCP metabolites and analogues and thus is used to detect and quantitate these substances in various body fluids and tissues.

Solid Dosage Form

Melting Point Determinations

The melting points for PCP were obtained from the Merck Index (1989). Bailey and Legault (1979) provided the melting point for the HCl of PCE. The melting points for the base forms of TCP, PCPy and TCPy were obtained from Bailey et al. (1976). Alvarez (1977) provided the melting point for the HCl of TCP.

Colour Tests

Colour tests performed on the pure hydrochloride of TCP and PCP included the Marquis test, Mecke's test and Mandelin's test (Alverez, 1977; Picard, 1976).

Additional References: Heagy, 1972.

Chromatography

Thin-Layer Chromatography

The following thin-layer chromatography systems are referenced in the data sheets for PCP and its analogues.

System A. Methylene chloride : n-butanol : aqueous ammonia (85:15:0.2), silica gel (Merck silica gel 60). Visualization using potassium iodoplatinate. (Cone et al., 1979)

System B. Methylene chloride : n-butanol : aqueous ammonia (85:15:0.2), silica gel (Quanta Gram). Visualization using potassium iodoplatinate. (Cone et al., 1979)

System C. Ethyl acetate : methanol : aqueous ammonia-water (29:1:0.25:0.5), glass fiber plates impregnated with silicic acid (Gelman ITLC-SA). Visualization using potassium iodoplatinate. (Cone et al., 1979)

System D. Ethyl acetate : methanol : dimethylamine (40% aqueous solution)(90:10:1.6), silica gel (Merck silica gel 60). Visualization using potassium iodoplatinate. (Cone et al., 1979)

System E. Ethyl acetate : methanol : diethylamine (90:10;1.6), silica gel (Merck silica gel 60). Visualization using potassium iodoplatinate. (Cone et al., 1979)

System F. Methanol : ammonia (100:1.5). Visualization with potassium iodoplatinate and ninhydrin. (Rao and Soni, 1983)

System G. Benzene : acetone : pyridine (16:8:1). Visualization with ninhydrin reagent and iodoplatinate. (Rao and Soni, 1983)

Additional References: Alvarez, 1977; Bailey et al., 1976; Picard, 1976; Shulgin and Helisten, 1975; White and Graves, 1978.

Gas Chromatography

Gas chromatographic data is expressed in terms of either retention time (RT) in minutes or retention time relative to phencyclidine (RRT). Below is a description of the GLC systems used. Systems A, B and C were obtained from Cone et al., (1979) and System D from Legault (1980).

System A.

Column. 1.8m x 2mm I.D. glass column packed with 3% SE-30 pm Gas-Chrom Q (100-120 mesh).
Column Temp. 170 °C.
Injection Temp. 160 °C
Carrier Gas: Nitrogen at a flow rate of 30 ml/min
Detector: Flame ionization.
Detector Temp. 250 °C.

System B.

Column. 1.8m x 2mm I.D. glass column packed with 3% OV-225 on Gas-Chrom Q (100-120 mesh).
Column Temp. 180 °C.
Injection Temp. 160 °C.
Carrier Gas: Nitrogen at a flow rate of 30 ml/min.
Detector: Flame ionization.
Detector Temp. 250 °C.

System C.

Column. 1.8m x 2mm I.D. glass column packed with 3% silar 5 CP on Gas-Chrom Q (100-120 mesh).
Column Temp. 180 °C.
Injection Temp. 250 °C.
Carrier Gas. Nitrogen at a flow rate of 30 ml/min.

Detector. Flame ionization.
Detector Temp. 250 °C.

System D.

Column. 4 ft glass column packed with 3% OV-7 (acid treated) on 80-100 mesh Chromosorb W.
Column Temp. 150 °C.
Injection Temp. 250 °C.
Carrier Gas. Helium at a flow rate of 30 ml/min.
Detector Temp. 275 °C.

Additional References: Alvarez, 1977; Bailey et al., 1976; Picard, 1976; Rao and Soni, 1983; Rao et al., 1980; Tycer and Finalet, 1977.

Spectroscopy/Spectrometry

Infrared Spectroscopy

The infrared (IR) spectra of the base and hydrochloride salts of PCP and its analogues were obtained from Rao et al. (1980). Infra-red spectra were recorded in potassium bromide.

Additional References: Alvarez, 1977; Bailey et al., 1976; Dobres, 1975; Heagy, 1972; Morris, 1977; Picard, 1976; Rao and Soni, 1983; Tycer and Finalet, 1977.

Ultraviolet Spectroscopy

Ultraviolet data for PCP, TCP, PCPy and TCPy were obtained from Bailey et al. (1976). Data for the HCl form of PCP and its analogues in an ethanol solution were recorded using a Beckman BD GT spectrophotometer. Ultraviolet data for PCE was obtained from Bailey and Legault (1979). Data for the HCl form of PCE in a methanol solution were recorded using a Beckman Acta CIII spectrophotometer. Data from both studies are expressed in terms of maximum absorbance wavelengths (in nm) with molar absorptivities provided in parentheses.

Additional References: Alvarez, 1977; Dobres, 1975; Heagy, 1972; Morris, 1977; Picard, 1976; Rao and Soni, 1983; Rao et al., 1980; Tycer and Finalet, 1977.

Mass Spectrometry

Mass spectra were obtained from Rao et al., (1980). using a Du Pont 21-490 mass spectrometer operating at 70 eV and interfaced with a gas chromatographic system.

Additional References: Bailey et al., 1976; Clark, 1987; Cone et al., 1979; Dobres, 1975; Heagy, 1972; Legault, 1980; Morris, 1977; Picard, 1976; Rao and Soni, 1983; Tycer and Finalet, 1977.

PHENCYCLIDINE

CAS Registry Numbers: 77-10-1 (Base); 956-90-1 (HCl)

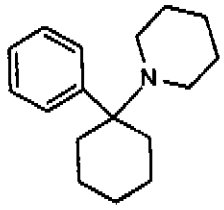
IUPAC Name: 1-(1-Phenylcyclohexyl)piperidine

CA Index Name: 1-(1-Phenylcyclohexyl)piperidine

Other Names: PCP; CI-395; GP 121; CL1; Hog; Peace Pill; Angel Dust; Crystal; Black Dust; Clickers; Sherms

International Control: II, 1971 Convention

Chemical Structure:



M.F.: $C_{17}H_{25}N$ **M.W.:** 243.38
$C_{17}H_{26}ClN$ (HCl) 279.85 (HCl)

Physical Appearance: Phencyclidine HCl is a white crystalline powder.

Chemical/Physical Properties.

M.P.: 46-46.5 °C (base); 233-235 °C (HCl)

Solubility: HCl form is soluble 1 in 6 of water, 1 in 7 of ethanol, 1 in 2 of chloroform and very slightly soluble in ether. (Moffat, 1986)

Colour Tests. Marquis - faint salmon with gas evolved.

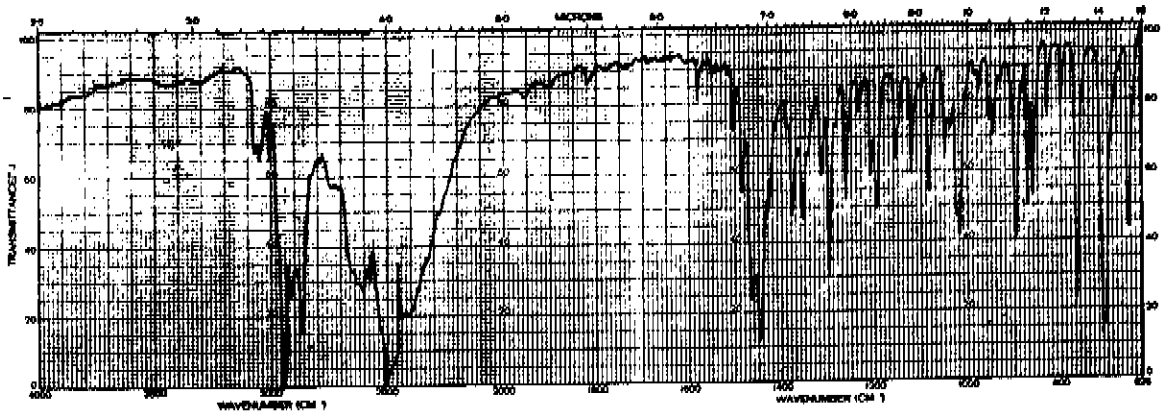
Thin-Layer Chromatography. System A - Rf 0.27; System B - Rf 0.58; System C - Rf 0.94; System D - Rf 0.70; System E - Rf 0.72; System F - Rf 0.55; System G - Rf 0.41.

Gas Chromatography. System A - RT 4.28; System B - RT 3.38; System C - RT 4.41; System D - RT 18.3.

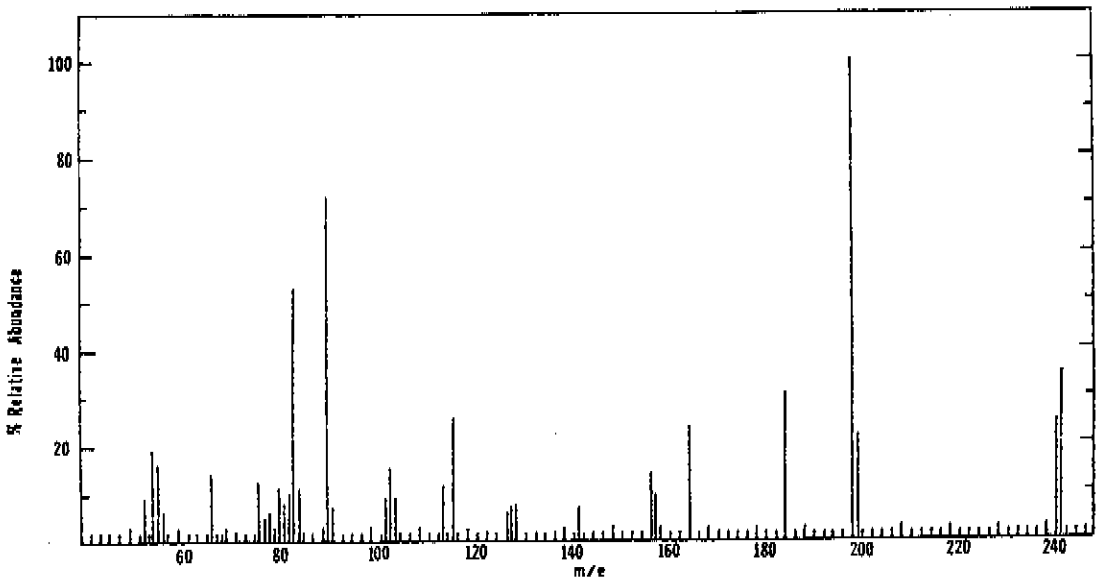
Ultraviolet Spectroscopy.

Neutral Solution - 251 nm (301), 256 nm (371), 261 nm (413), 268 nm (322)

Infrared Spectrum.
HCl



Mass Spectrum.



N-ETHYL-1-PHENYLCYCLOHEXYLAMINE

CAS Registry Number: 2201-15-2

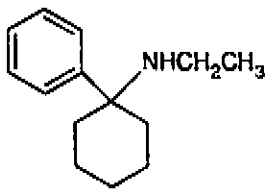
IUPAC Name: N-Ethyl-1-phenylcyclohexylamine

CA Index Name: N-Ethyl-1-phenylcyclohexylamine

Other Names: Eticyclidine
Cyclohexanamine
Ethylphencyclidine
PCE; CL45; CI-400; Rocket Fuel

International Control: I, 1971 Convention

Chemical Structure:



M.F.: $C_{14}H_{21}N$ **M.W.:** 203.3

Chemical/Physical Properties.

M.P.: 233-236 °C (HCl)

Thin-Layer Chromatography. System A - Rf 0.25; System B - Rf 0.45; System C - Rf 0.80; System D - Rf 0.60; System E - Rf 0.43; System F - 0.44.

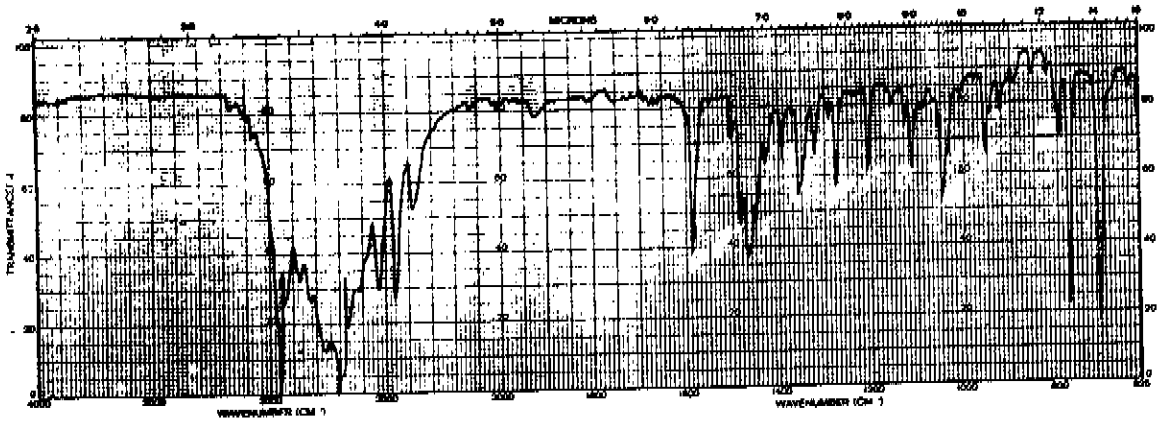
Gas Chromatography. System A - RRT 0.29; System B - RRT 0.30; System C - RRT 0.31.

Ultraviolet Spectroscopy.

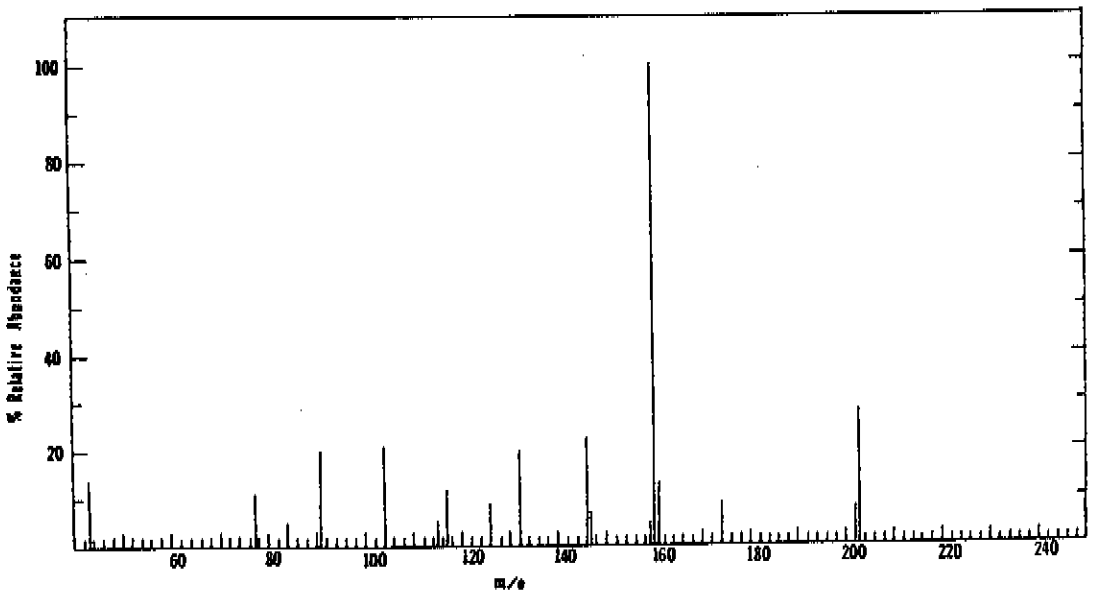
Neutral Solution - 251 nm (160), 257 nm (215), 261 nm (186), 267 nm (127)

Infrared Spectrum.

HCl



Mass Spectrum.



N-(1-(2-THIENYL)CYCLOHEXYL)PIPERIDINE

CAS Registry Number: 21500-98-1

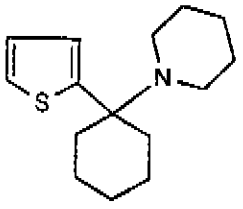
IUPAC Name: N-(1-(2-Thienyl)cyclohexyl)piperidine

CA Index Name: N-(1-(2-Thienyl)cyclohexyl)piperidine

Other Names: Tenocyclidine
Thienylphencyclidine
TCP; CL-15; CN-26; CI-421

International Control: I, 1971 Convention

Chemical Structure.



M.F.: $C_{15}H_{23}NS$ **M.W.:** 249.41
$C_{15}H_{24}ClNS$ 285.85 (HCl)

Physical Appearance: Base is a viscous, light yellow oil. HCl appears as a fine, white, crystalline powder.

Chemical/Physical Properties.

M.P.: 200-203 °C (Base, sublimation); 233-236 °C (HCl) (With transition at 182-183 °C).

Solubility: Base is soluble in chloroform, ether and hexane. HCl is soluble in chloroform and water, but insoluble in hexane and ether.

Colour Tests. Marquis - faint pink to grey brown or grey orange.
Mecke's - yellow green --> blue-green --> deep blue.
Mandelin - green.

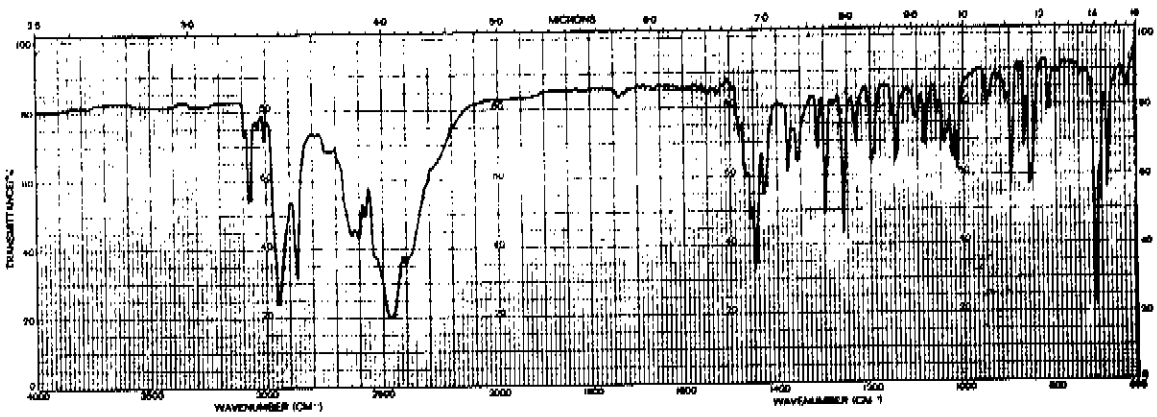
Thin-Layer Chromatography. System A - Rf 0.54; System B - Rf 0.75; System C - Rf 90; System D - Rf 85; System E - Rf 0.84; System F - Rf 0.63; System G - Rf 0.42.

Gas Chromatography. System A - RRT 0.17; System B - RRT 0.22; System C -RRT 0.26; System D - RT 18.3.

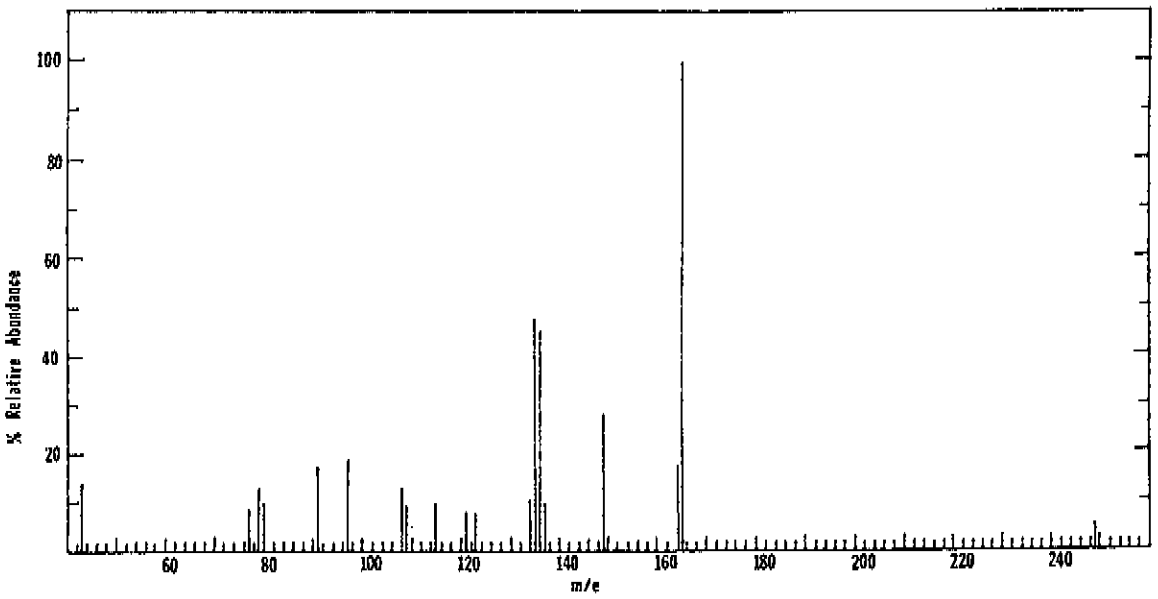
Ultraviolet Spectrum.

Neutral Solution - 232 nm (7933)

Infrared Spectrum.
HCl



Mass Spectrum.



1-(1-PHENYLCYCLOHEXYL)PYRROLIDINE

CAS Registry Number: 2201-39-0

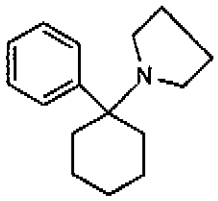
IUPAC Name: 1-(1-Phenylcyclohexyl)pyrrolidine

CA Index Name: 1-(1-Phenylcyclohexyl)pyrrolidine

Other Names: Rolicyclidine
PCPy, PHP

International Control: I, 1971 Convention

Chemical Structure:



M.F.: $C_{16}H_{23}N$ **M.W.:** 229.36

Chemical/Physical Properties.

M.P: 221-222 °C (sublimation)

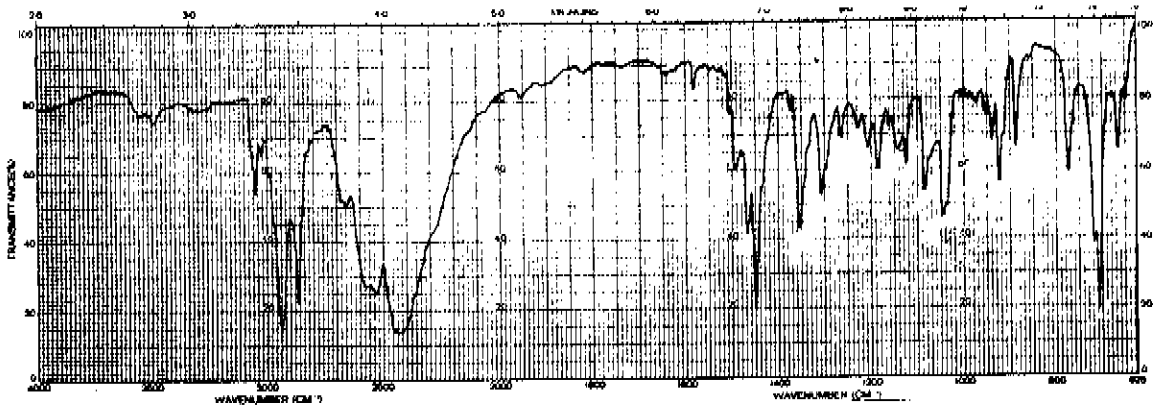
Thin-Layer Chromatography. System A - Rf 0.11; System B - Rf 0.23; System C - Rf 71; System D - Rf 40; System E - RF 26; System F - Rf 0.31

Gas Chromatography. System A - RRT 0.74; System B - RRT 0.77; System C -RRT 0.78; System D - RT 12.6.

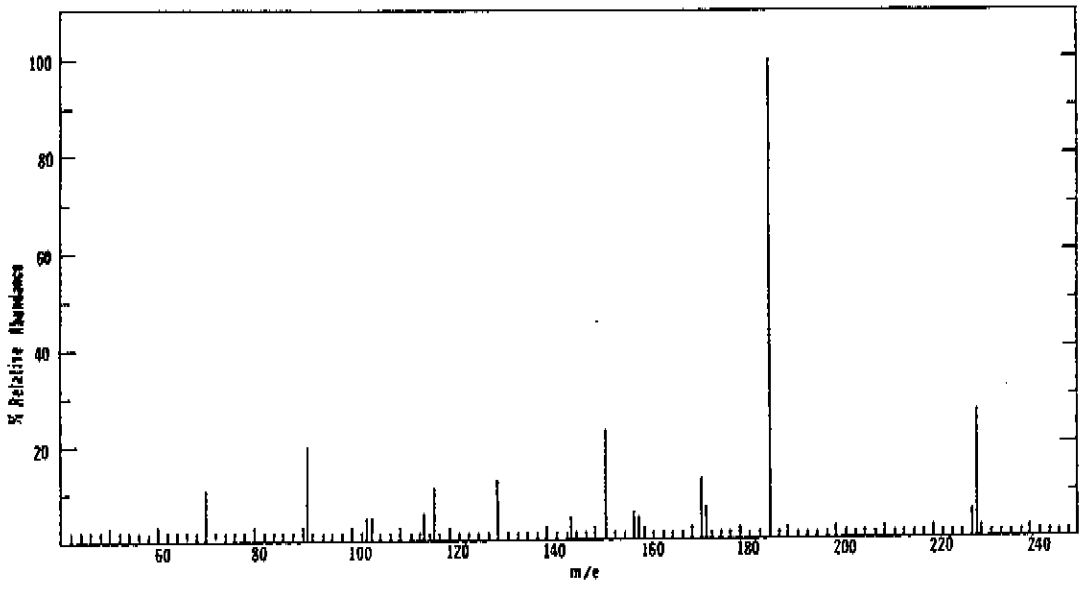
Ultraviolet Spectroscopy.

Neutral Solution - 251 nm (247), 256 nm (327), 261 nm (373), 268 nm (293)

Infrared Spectrum.
HCl



Mass Spectrum.



1-(1-(2-THIENYL)CYCLOHEXYL)PYRROLIDINE

CAS Registry Number: 22912-13-6

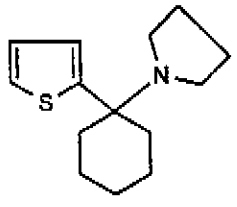
IUPAC Name: 1-(1-(2-Thienyl)cyclohexyl)pyrrolidine

CA Index Name: 1-(1-(2-Thienyl)cyclohexyl)pyrrolidine

Other Names: N-(1-(2-Thienyl)cyclohexyl)pyrrolidine
TCPy

International Control: Not Scheduled.

Chemical Structure:



M.F.: $C_{14}H_{21}NS$ **M.W.:** 235.40

Chemical/Physical Properties.

M.P.: 187-188 °C

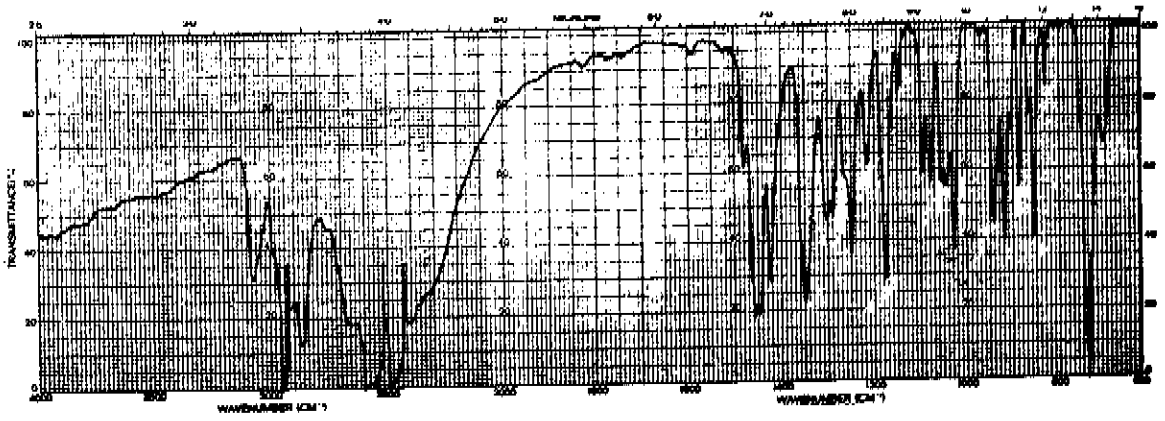
Thin-Layer Chromatography. System F - Rf 0.48; System G - Rf 0.27.

Gas Chromatography. System D - RT 11.9 min.

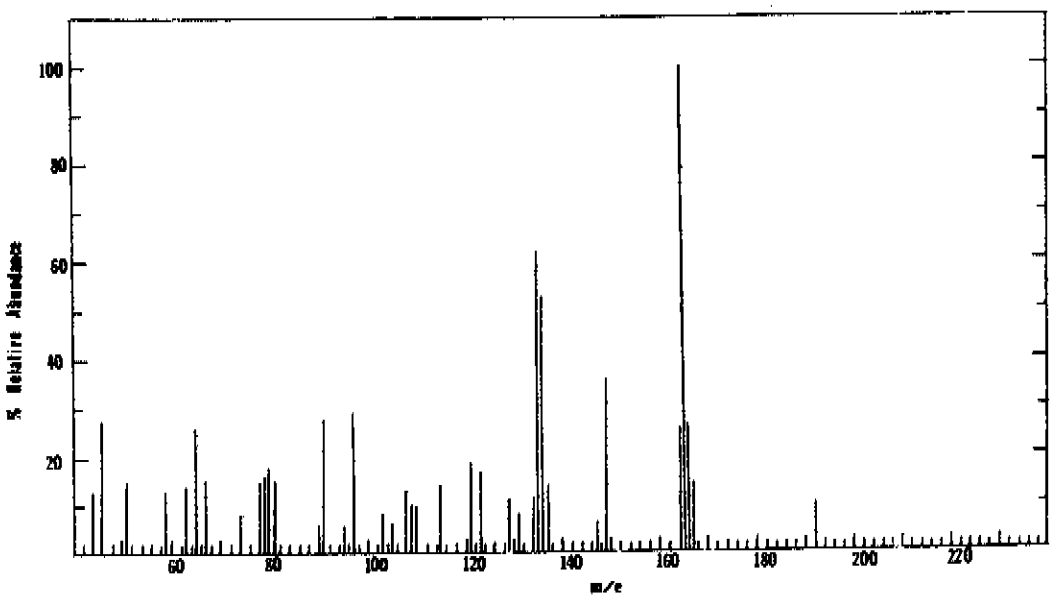
Ultraviolet Spectroscopy.

Neutral Solution - 232 nm (7837)

Infrared Spectrum.
HCl



Mass Spectrum.



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AMINOREX AND 4-METHYLAMINOREX

GENERAL STATEMENT OF THE PROBLEM

Aminorex and 4-methylaminorex are two new designer drugs that are easily made in clandestine laboratories from readily available chemicals. Both drugs are central nervous system stimulants with pharmacological properties similar to the amfetamines. They are promoted in the illicit drug market as new drugs which produce effects between cocaine and amfetamine. These drugs have appeared sporadically in the United States and Canada and have been associated with a few cases of suspected overdose. Because these substances are easily synthesized, they could become low cost substitutes for other stimulants such as cocaine or methamfetamine in the international illicit drug market.

GENERAL HISTORY

Legitimate Use

Aminorex and 4-methylaminorex belong to a class of compounds called oxazolines which were first synthesized by McNeil Laboratories in the early 1960's. They were found to be potent appetite suppressants and central nervous system (CNS) stimulants. After extensive testing in animals and human subjects, aminorex was introduced in Europe in 1965 as a prescription drug (Menocil and Apiquel) for weight reduction. Three years later the drug was withdrawn from clinical use because it caused fatal pulmonary hypertension in some subjects. Since that time, neither aminorex nor 4-methylaminorex have been further developed as pharmaceuticals.

Illicit Use

4-Methylaminorex was first reported in the illicit drug traffic in Florida in 1985 and 1986. It 1987 it was detected in paraphernalia and body fluids associated with a drug overdose victim in Florida. Since 1986, law enforcement officials in the U.S. have seized the drug in California, Florida, Indiana, New Jersey and Pennsylvania. 4-Methylaminorex has also been identified in drug evidence submissions in Canada. Four clandestine laboratories were seized which were manufacturing 4-methylaminorex from phenylpropanolamine. 4-Methylaminorex produced in this way is the racemic cis isomeric form.

4-Methylaminorex is occasionally sold as "speed", but more often is sold under the rather unique names "EU4EA", "U4EA", or "U4Euh". There have been recent reports that the drug is being sold as "Ice" or "Blue Ice", street names also associated with dextro-methamfetamine hydrochloride. Aminorex has also been identified by forensic laboratories in the U.S. the last few years. Analysis of recently seized drugs revealod they sometimes contained both aminorex and 4-methylaminorex.

PHARMACOLOGY

General Effects

Aminorex and 4-methylaminorex produce all the effects of central nervous system stimulants. With respect to central nervous system activity, they have approximately one-half to one third the potency of d-amfetamine and a slightly shorter duration of action. Restlessness and increased alertness are the first behavioral signs noted. Other effects observed include dry mouth, loss of appetite, insomnia and analgesia. At higher doses there is an increase in motor activity which may be followed by ataxia, tremors and seizures.

The aminorex compounds, like the amfetamines, stimulate both the central and the peripheral nervous systems; however, these two classes of drugs may have somewhat different mechanisms of action. The amfetamines stimulate both the central and peripheral nervous systems indirectly by triggering the release from nerve terminals of endogenous catecholamines like epinephrine and norepinephrine which, in turn, produces the pharmacological effects. Aminorex and its derivatives stimulate the peripheral nervous system in a similar manner by causing the release of catecholamines; however, studies in experimental animals suggest that the aminorex compounds stimulate the central nervous system directly.

The addiction liability of the aminorex compounds appears to be qualitatively similar to that of the amfetamines. Animals trained to discriminate d-amfetamine from saline recognize 4-methylaminorex as being amfetamine-like. Animals tolerant to amfetamine are cross tolerant to 4-methylaminorex. Animals trained to lever-press for cocaine will self administer 4-methylaminorex, thus providing evidence of positive reinforcing effects.

Structure Activity Relationships

4-Methylaminorex is structurally similar to other CNS stimulants, such as amfetamine, pemoline and aminorex in that they all contain a beta-phenylethylamine moiety, a basic structure for the production of central nervous system stimulation by sympathomimetic amines. Thus, they all share a common CNS stimulant action. In fact, the structure activity relationships for the aminorex compounds appear to be similar to those for the amfetamines. Preliminary pharmacological data for over two dozen aminorex analogues have been reported. The greatest potency is achieved when halogens, such as bromine, chlorine, and fluorine are substituted on the phenyl ring of aminorex. Para-fluoroaminorex is the most potent analogue found to date. It is approximately four times more potent than aminorex or slightly more potent than amfetamine. Unlike amfetamine, in which the d isomer is significantly more active than the l isomer as a stimulant, all stereoisomers of the aminorex compounds appear to be active. The importance of the amino versus the imino tautomer is not known. An earlier report suggested that the amino tautomer is the most stable form, but a more recent paper suggests the imino tautomer predominates.

Routes of Administration and Dosage Forms

Little is known about how aminorex and 4-methylaminorex are actually used on the street. Since they are most likely used as substitutes for amfetamine or cocaine, they are probably taken orally, intranasally ("snorting"), and via inhalation (smoking). Intravenous use is less likely because of the low solubility of the bases in water. Because aminorex and 4-methylaminorex are sold in free base form, they can be smoked without conversion from the salt to free base form (as must be done with methamfetamine and cocaine).

Aminorex was prescribed as an appetite suppressant at doses of 10 to 20 milligrams per day. It is likely that street doses are higher - perhaps 25 to 30 milligrams - so as to produce the desired stimulant effect. Also, because tolerance can develop rapidly to these drugs, much higher doses are likely to be ingested by some individuals.

Pharmacokinetics

Aminorex and 4-methylaminorex were developed before sophisticated methods for pharmacokinetic analysis were available; thus, the data available on their absorption, distribution, metabolism and elimination are limited. Although these two drugs are pharmacologically similar to the amfetamines, their chemical structures are perhaps more similar to stimulants like pemoline. The limited data available suggests that their biological fate may be similar to both pemoline and amfetamine.

In humans the absorption of aminorex is relatively rapid with most of the drug being absorbed by 3 to 4 hours. Early clinical studies showed that a single 15 mg oral dose of aminorex, produces a peak plasma concentration of around 40 ug/ml within two hours. Subsequently, the concentration declines slowly, with drug still being detectable at a concentration of around 5 ug/ml at 24 hours. The absorption of 4-methylaminorex in humans has not been examined; however, it is likely that the absorption of 4-methylaminorex will be similar to that of aminorex.

Studies in experimental animals do not reveal any unusual accumulation of aminorex in any tissue. The organs of elimination, the liver and kidneys, have the highest concentration of drug. Some drug is retained in the gastrointestinal tract, probably the result of incomplete absorption.

The metabolic fate of aminorex and 4-methylaminorex has been examined only to a limited extent. Available evidence indicates that these drugs are metabolized via oxidative deamination and aromatic hydroxylation, two pathways typical of amfetamines. In man oxidation of the amine functional group of aminorex produces an oxazolidinone metabolite, which is subsequently converted to a beta-hydroxyphenyl urea by cleavage of the ring. In laboratory animals, 4-methylaminorex undergoes deamination to produce a 2-oxazolidinone metabolite, aromatic hydroxylation to produce 2-amino-5-(p-hydroxyphenyl)-4-methyl-2-oxazoline and hydrolysis to yield phenylpropanolamine. The metabolic fate of 4-methylaminorex in humans is not known.

Aminorex and 4-methylaminorex are eliminated from the blood by a combination of liver metabolism and excretion by the kidneys. Elimination via the bile into the intestines seems to be a relatively minor route. Both drugs are eliminated in urine primarily as unchanged drug. The reported half-life for aminorex in humans is 7.7 hours. There is no available data on the half-life of 4-methylaminorex in humans.

TOXICOLOGY

Toxic Clinical Manifestations of Drug Use and Overdose

The acute toxicity of aminorex and 4-methylaminorex should be qualitatively similar to that of amfetamine and would result from overstimulation of the central nervous system. Low doses produce mental alertness and loss of appetite,

while higher doses produce restlessness and increased motor movement. Further increases in the dose will cause agitation, increased heart rate, rapid breathing, tremors and possible convulsions. Convulsive episodes may be followed by loss of consciousness, depressed respiration and death. Studies in experimental animals suggest that aminorex and 4-methylaminorex, in contrast to amfetamine, have a low therapeutic index relative to the production of seizures. If aminorex and amfetamine toxicity are similar, then a delayed set of toxic signs may appear a few days later. In these later stages of acute intoxication, hallucinations, hyperthermia and fluctuations in blood pressure may occur which may be lifethreatening.

Prolonged use of high doses of aminorex compounds may lead to "amfetamine psychosis" and lung toxicity. Signs and symptoms typical of "amfetamine psychosis" include extreme agitation, hallucinations and paranoia. Lung toxicity characterized as pulmonary hypertension, is potentially the greatest health risk since it may result from chronic use of low doses. When aminorex was first used as an appetite suppressant, the incidence of lung toxicity was rare (approximately 1/1000) but often fatal. The risk may be greater when the drug is used at higher doses as a stimulant or when it is ingested by smoking. Dyspnea following exertion was the earliest symptom reported by individuals who suffered pulmonary hypertension after taking the prescription drug aminorex. This was followed by angina pectoris (shooting pains in the upper arm and shoulder) and fainting spells. These conditions may worsen for months, even years, with some patients dying of heart failure or pulmonary thromboembolism (blood clot in the lung). Clinical and animals studies have failed to elucidate the mechanism(s) by which aminorex produces pulmonary hypertension. It is not known whether 4-methylaminorex also causes pulmonary hypertension.

Forensic Toxicology

There have been two suspected cases of overdose from 4-methylaminorex with one of these cases reported in the literature. No details of the autopsy findings were given but a description of the scene suggested that death was the result of an acute drug overdose. The concentration of 4-methylaminorex found in blood was 21.3 ug/ml compared with 12.3 ug/ml found in urine.

CLINICAL MANAGEMENT

Until there is more information on the pharmacology and toxicology of the aminorex compounds, or more clinical experience in treating overdose cases, it seems prudent to consider them as amfetamine-like compounds and treat accordingly.

The prevention and control of seizures should be the initial objective in treating the acute toxicity of aminorex and 4-methylaminorex. This should be followed by efforts to prevent the delayed toxicity; that is, maintaining normal body temperature (external cooling with ice packs if necessary) and maintaining normal blood pressure (fluid replacement, and possibly medications to control blood pressure).

Treatment of aminorex-induced toxic psychosis requires long-term care by specialists experienced in the medical management of psychiatric patients. Similarly, treatment of pulmonary toxicity from the aminorex compounds requires long-term treatment by specialists in cardiovascular medicine.

CLANDESTINE SYNTHESIS

Synthesis I

A variety of aminorex-like compounds (oxazolines) can be prepared quite easily by reacting a suitable amino alcohol with cyanogen bromide. 4-Methylaminorex can exist as four stereoisomers and two racemates. Each can be prepared by condensation of the respective 2-amino-1-phenylpropanol with cyanogen bromide. The cis racemate is the form identified in illicit drug seizures and is produced from phenylpropanolamine (norephedrine). The trans isomers are prepared from norpseudoephedrine. dl-2-Amino-1-phenylethanol is used as the starting material for dl-aminorex.

Synthesis II

An alternative synthesis utilizes the reaction of the appropriate amino alcohol with a suitable isocyanate to produce a hydroxyurea. The hydroxyurea is then converted to a chlorourea with thionyl chloride which is then cyclized to the oxazoline by boiling in water. This is a more complicated process, but useful for producing aminorex analogues substituted at the 2-amino position.

Precursors and Essential Chemicals

2-Amino-1-phenylpropanol(phenylpropanolamine) or 2-Amino-1-phenylethanol (I,II)
Cyanogen bromide (I)
Sodium acetate (I)
Hydroxyurea (II)
Thionyl chloride (II)

ANALYTICAL CHEMISTRY

Body Fluids

Immunoassay

Neither aminorex or 4-methylaminorex are detectable using available radioimmunoassays (RIA), the fluorescence polarization assay (TDX), or the enzyme multiplied immunoassay technique (EMIT)) for amfetamine-like substances (Smith and Kidwell, 1989).

Chromatography

Davis and Brewster (1988) described a blood and urine extraction procedure for 4-methylaminorex. Gas chromatographic analysis was performed using a Hewlett Packard 5890 gas chromatograph equipped with a capillary column and a flame ionization detector.

Spectrometry

Davis and Brewster (1988) described a GC/MS method for analyzing 4-methylaminorex in urine obtained from an overdose victim. After an acid/base extraction, an aliquot of the chloroform extract was analyzed using a Hewlett Packard 5890 gas chromatograph equipped with a 10 m methylsilicone narrow bore capillary column interfaced with a mass selective detector.

Smith and Kidwell (1989) have described a method for the GC/MS analysis of 4-methylaminorex using pentafluoropropanyl anhydride derivatization. The limit of detection for this method is reported to be 50 ng/ml.

Quantitation

The gas chromatography procedure described by Davis and Brewster (1988) using methaqualone as an internal standard has been used for the quantitation of 4-methylaminorex after extraction from blood and urine.

Solid Dosage Forms

Since only the cis-4-methylaminorex is controlled under the 1971 Convention, it is critical for the forensic chemist to differentiate between the cis and trans forms.

Melting Point Determinations

The melting point of aminorex was obtained from Klein and Morello (1990). The melting points of various 4-methylaminorex stereoisomers were obtained from Klein et al. (1989) and Poos et al. (1963). Melting points of other stereoisomers of 4-methylaminorex have been reported by Wollweber et al. (1980).

Colour Tests

The addition of the free bases of aminorex and 4-methylaminorex in 0.5 ml of ethanol to 2 % aqueous cobalt thiocyanate ($Co(SCN)_2$) gives a positive colour reaction (Klein and Morello, 1990; Klein et al., 1989). 4-Methylaminorex hydrochloride will produce a positive colour reaction only after addition of saturated aqueous sodium carbonate (Klein et al., 1989).

Additional References: Inaba and Brewer (1987).

Chromatography

Thin-Layer Chromatography

The following solvent systems were used to attempt to separate the free base cis-(4*S*, 5*R*) and trans-(4*R*, 5*R*) isomers of 4-methylaminorex. Hydrochlorides produced multiple spots and streaking (Klein, 1989).

System A: Ethyl acetate : ethanol : ammonium hydroxide (86:10:4), silica gel IB-F plates (Klein et al., 1989)

System B: Ammonium hydroxide saturated chloroform : methanol (9:1), silica gel IB-F plates (Klein et al., 1989)

System C: Ethyl acetate : ethanol : ammonium hydroxide (86:10:4), alumina IB-F plates (Klein et al., 1989)

System D: Ammonium hydroxide saturated chloroform : methanol (9:1), alumina IB-F plates (Klein et al., 1989)

System E: Isopropanol : water : ammonium hydroxide (72:24:4), C_{18} reverse phase plates (Klein et al., 1989)

Gas Chromatography

Gas chromatographic analyses of the bases and hydrochlorides were performed on a Perkin-Elmer Sigma 2000 Capillary Chromatograph (Klein, 1989). Values are expressed as actual retention times in minutes. Klein (1989) presents GC data for the four stereoisomers and two racemates of 4-methylaminorex; however, only data for the dl-cis and dl-trans isomers are provided in this manual. The dl-cis form of 4-methylaminorex is the one found in the illicit traffic. The hydrochlorides undergo extensive thermal decomposition and produce more complex, and thus, less useful, chromatograms. The free bases are still apparent in the chromatograms. The following conditions were employed:

Column. DB-1 30 m by 0.25 mm capillary column coated with a 0.25 um film thickness (J & W Scientific)
Temperatures. Column - 140 °C initial (held 1 minute), programmed increase of 4 °C/min. to 200 °C; Injector - 280 °C.
Carrier Gas. Hydrogen at a flow rate of 46.5 cm/sec.
Detector. Flame ionization

Additional References: Davis and Brewster (1988); Inaba and Brewer, 1987.

Spectroscopy/Spectrometry

Ultraviolet Spectroscopy

Ultraviolet spectroscopy data for aminorex and 4-methylaminorex in methanol and sulfuric acid solutions are reported as wavelengths of maximum absorbance (CND, 1990; Davis and Brewster, 1988).

Additional References: By et al., 1989

Infrared Spectroscopy

Infrared spectra of aminorex and the bases and hydrochlorides of the cis and trans stereoisomers of 4-methylaminorex were recorded from KBr discs using a fourier transform spectrophotometer. The infrared spectrum of the dl-base of aminorex was obtained from Klein (1989). The cis and trans stereoisomers of the base and HCl forms of 4-methylaminorex were obtained from Analytical Profiles of Methylaminorex and Designer Analogues published by CND Analytical Inc. The cis and trans stereoisomers of 4-methylaminorex display similar but distinct spectra.

Additional References: By et al., 1989; Davis and Brewster, 1988; Inaba and Brewer, 1987; and Klein and Morello, 1990.

Mass Spectrometry

The mass spectrum of aminorex was obtained from Analytical Profiles of Methylaminorex and Designer Analogues published by CND Analytical. The mass spectum was recorded using an electron impact instrument at 70 eV interfaced with a GC equipped with a 12 m x 0.31 mm inside diameter column using a 0.52 um thickness of OV-1. The column temperature was programmed.

The mass spectra of 4-methylaminorex were obtained using a Finnigan-MAT 8320 Mass Spectrometer at 70 eV (resolution = 7500; 5% valley)(Klein et al., 1989). Samples were run using the solid probe inlet.

It should be noted that the cis and trans isomers give nearly identical spectra.

Additional References: Inaba and Brewer, 1990; Davis and Brewster, 1988 and By et al., 1989.

NMR (Klein et al., 1989; By et al., 1989) may also be used to differentiate the cis- and trans- isomers of 4-methylaminorex. Microcrystalline tests (platinum chloride and gold chloride) are also effective provided that direct comparison to standards are made (Klein et al., 1989).

AMINOREX

CAS Registry Number: 2207-50-3

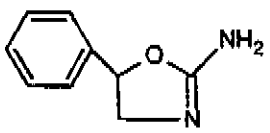
IUPAC Name: 2-Amino-5-phenyl-delta^2-oxazoline

CA Index Name: 4,5-Dihydro-5-phenyl-2-oxazolamine

Other Names: 2-Amino-5-phenyl-2-oxazoline
Aminoxaphen; McNeil 742

International Control: Not controlled

Chemical Structure:



M.F.: $C_9H_{10}N_2O$ **M.W.:** 162.19

Physical Appearance: Free base is a white, crystalline powder (recrystallized from carbon tetrachloride/ethyl acetate (5:1)) or white iridescent flakes (recrystallized from water). Hydrates are not formed.

Chemical/Physical Properties.

M.P.: 136-138 °C (broad melting range; i.e., gradual breakdown of crystal structure observed over final 10 °C with complete dissolution occurring over the final 2# C).

Stereochemistry: Aminorex has one asymmetric carbon and may exist as two enantiomers and a racemate.

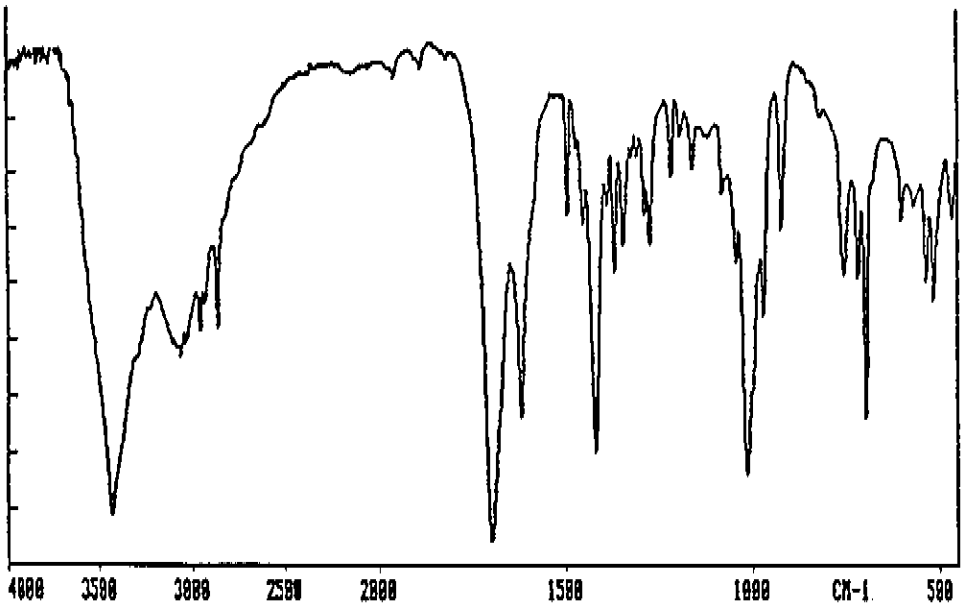
Colour Tests: Cobalt thiocyanate - instantaneous deep blue

Gas Chromatography. RT 6.23 min

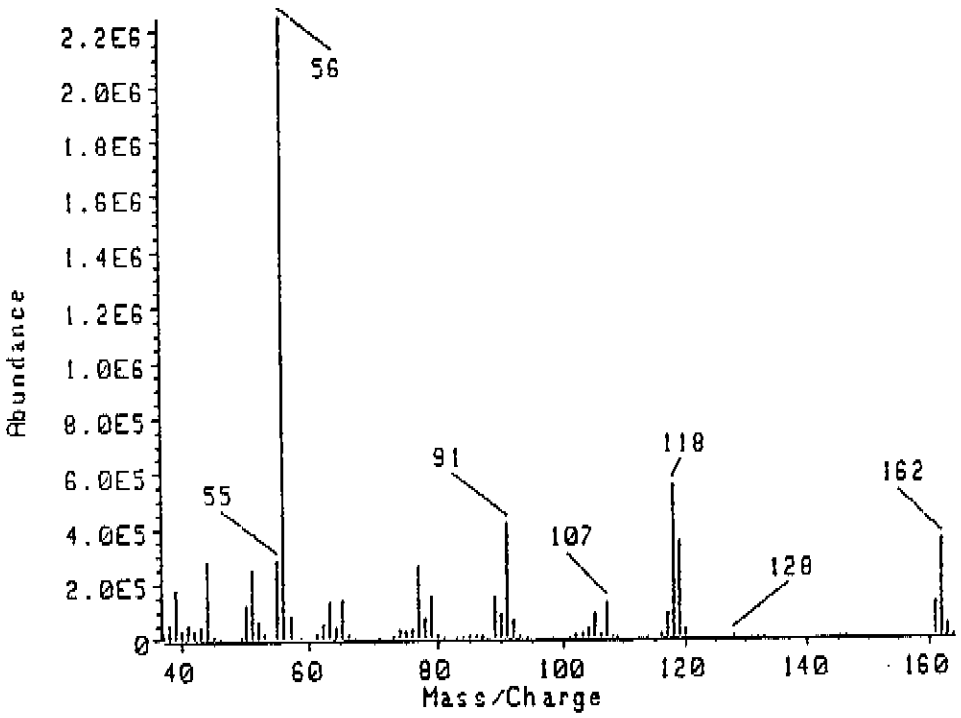
Ultraviolet Spectroscopy.

Neutral and acidic solutions - 251 nm, 257 nm, 262 nm, 268 nm

Infrared Spectrum.
dl-Base



Mass Spectrum.



4-METHYLAMINOREX

CAS Registry Number: 3568-94-3; individual isomers have specific CAS registry numbers as follow: 29493-77-4; 27780-30-9; 75493-87-7; 42510-77-0; 2077-59-0

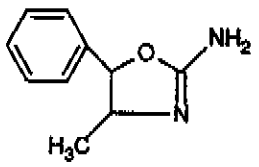
IUPAC Name: 2-Amino-4-methyl-5-phenyl-2-oxazoline

CA Index Name: 4,5-Dihydro-4-methyl-5-phenyl-2-oxazolamine

Other Names: 2-Amino-4-methyl-5-phenyl-delta^2-oxazoline
d,l-cis-2-Amino-4-methyl-5-phenyl-2-oxazoline
d,l-erythro-2-Amino-4-methyl-5-phenyl-2-oxazoline
NcN-822; Euphoria; U4Euh; ICE; Blue Ice; 4-MAX

International Control: I, 1971 Convention (Only cis-4-methylaminorex is controlled.)

Chemical Structure.



M.F.: $C_{10}H_{12}N_2O$ **M.W.:** 176.22

Physical Appearance: Bases (recrystallized from chloroform/carbon tetrachloride (1:1)) are white crystalline powders. Hydrochlorides (recrystallized from isopropanol/chloroform/diethyl ether (1:1:1)) are white crystalline powders except the dl-trans hydrochloride which is hygroscopic and is an amorphous solid.

Chemical/Physical Properties.

M.P.: d,l-cis base (hydrate) - 154-156.5 °C
d,l-cis free base - 139-142 °C
d,l-cis HCl - 178-180 °C
d,l-trans free base - 148-150 °C; 150-152 °C
d,l-trans HCl - 132-136 °C (amorphous solid)

Solubility: Sparingly soluble in water.

Stereochemistry: 4-Methylaminorex has two asymmetric carbon atoms and may exist as four possible stereoisomers (trans-(4R, 5R), trans-(4S, 5S), cis-(4R, 5S) and cis-(4S, 5R)) and two racemates (dl-cis and dl-trans).

Colour Tests: Cobalt thiocyanate - instantaneous deep blue (base);
Cobalt thiocyanate - no colour change (HCl) - addition of one drop of saturated aqueous sodium carbonate precipitates a blue solid

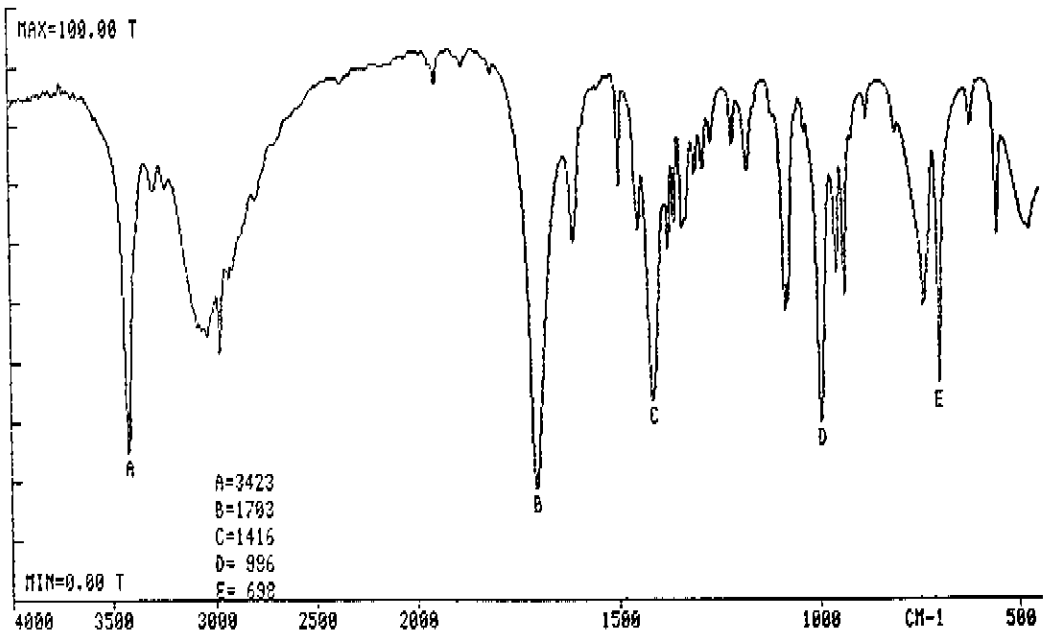
Thin-Layer Chromatography. System A - Rf 0.42 (trans), 0.40 (cis); System B - Rf 0.57 (trans), 0.50 (cis); System C - Rf 0.55 (trans), 0.51 (cis); System D - Rf 0.66 (trans), 0.64 (cis); System E - Rf 0.59 (trans), 0.59 (cis)

Gas Chromatography. RT 5.67 (trans base), 5.62 (trans HCl) (with decomposition); RT 6.10 (cis base), 6.04 (cis HCl) (with decomposition).

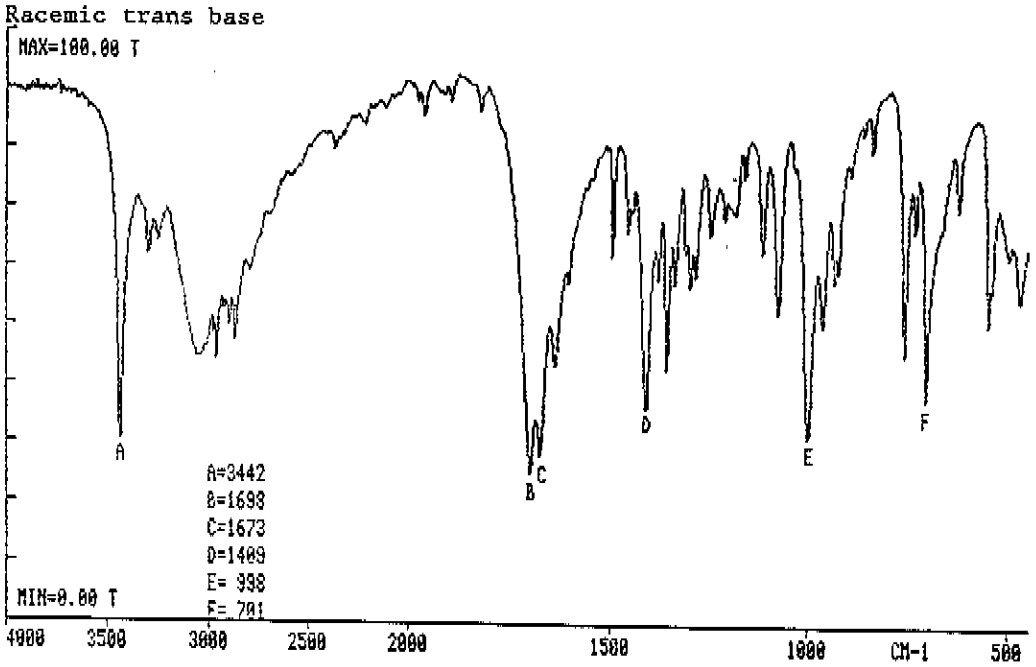
Ultraviolet Spectroscopy:

Neutral and acidic solutions - 251 nm, 257 nm, 262 nm, 268 nm

Infrared Spectra.
Racemic cis-base



Racemic trans base



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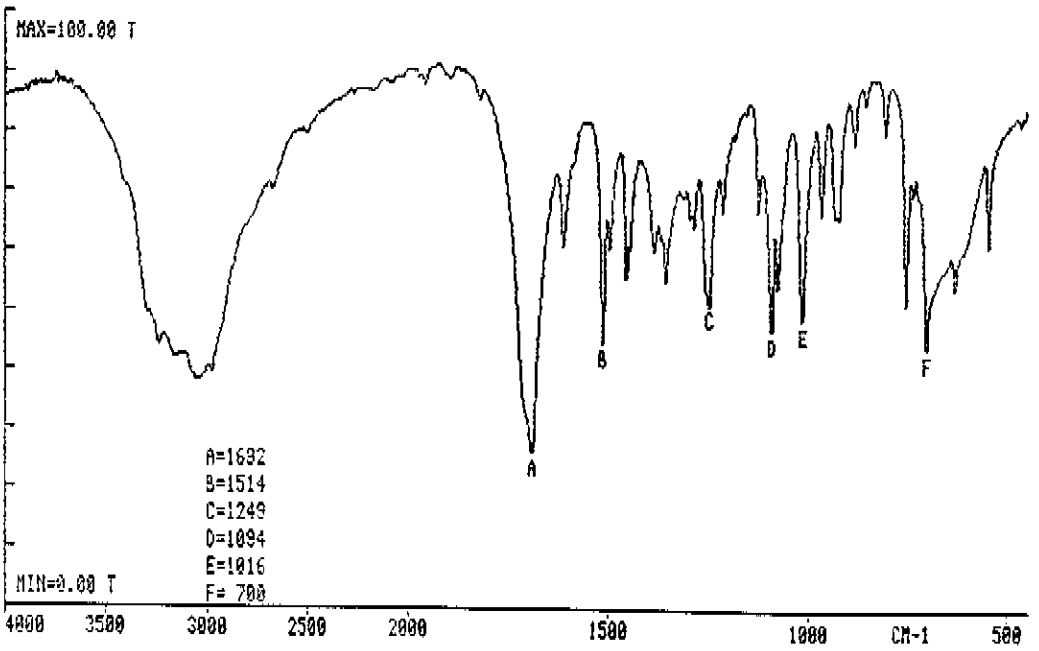
Racemic cis Hydrochloride



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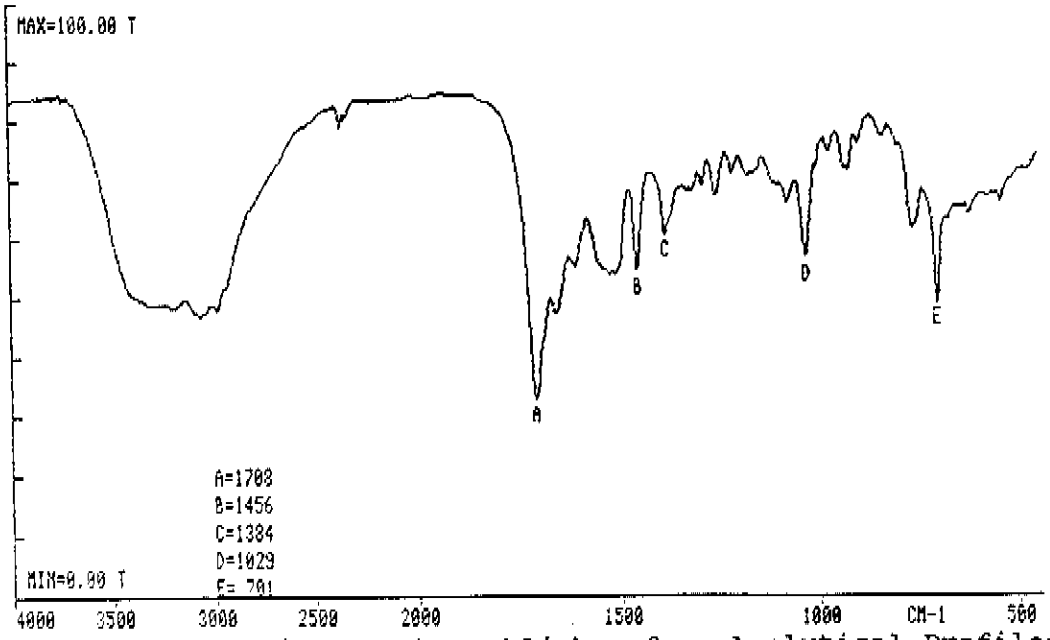
Racemic trans Hydrochloride



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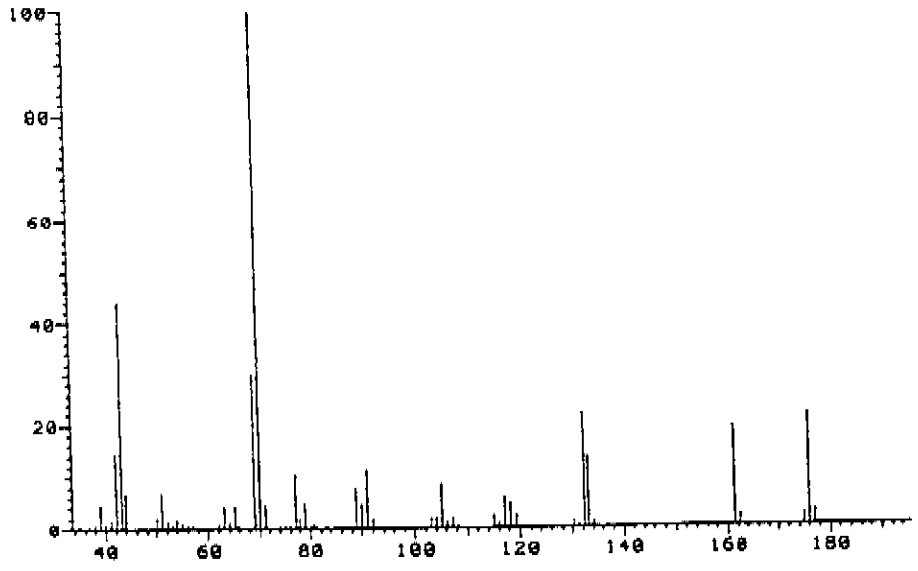
Mass Spectra.

Racemic trans



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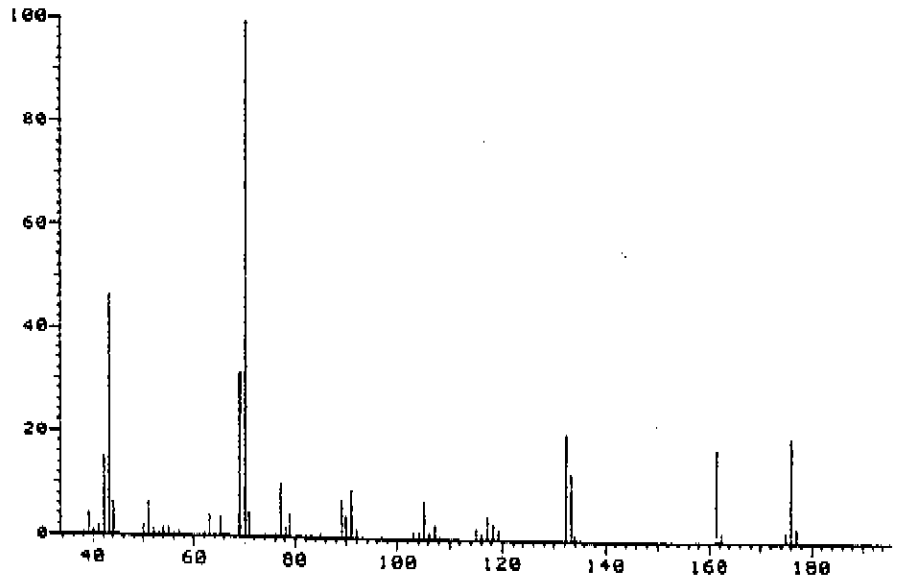
Racemic cis



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