DIVISION OF NARCOTIC DRUGS
Vienna

RECOMMENDED METHODS FOR TESTING ILLICIT RING-SUBSTITUTED AMPHETAMINE DERIVATIVES

MANUAL FOR USE BY NATIONAL NARCOTICS LABORATORIES

UNITED NATIONS
New York, 1987

ST/NAR/12

C O N T E N T S

INTRODUCTION

Background

Over the past few years there has been a considerable increase in the number of scheduled substances newly included under international control. This increase reflects a rapid diversification of drugs of abuse, and the consequent increase of regulatory efforts results in turn in a larger number of controlled substances and in better but, at the same time, more stringent national legislation and sentencing provisions. At the same time, the seized quantities of drugs already under control, such as the opiates, cocaine and coca paste, cannabis products, amphetamine and related compounds has also shown an alarming and unprecedented increase in certain regions. This new situation, involving an increase both in the frequency and volume of seizures, presents a challenge not only to national law enforcement authorities, but also to the technical and scientific staff of forensic laboratories.

Owing to the ingenuity of illicit producers and promoters, unexpected new illicit drugs or combinations of drugs appear on the illicit market, requiring rapid and adequate action as well as ingenuity on the part of forensic chemists. Similarly, the increased number of controlled substances and of related legislative provisions place additional pressure on national forensic and narcotic laboratories and their staff. Analysts have to be able to deal with more substances and preparations and to use faster, more accurate and more specific methods of identification and analysis. In addition, the international character of drug trafficking requires the speedy exchange of analytical data between laboratories and law enforcement authorities both on the national and the international levels. Development of internationally acceptable methods of testing would contribute greatly to the achievement of these objectives, and this possibility has been under consideration for some time.

At its thirty-second session in February 1987, the Commission on Narcotic Drugs reviewed the implementation of the International Drug Abuse Control Strategy and five-year programme of action with special emphasis on technical and scientific projects. It stressed the importance of timely exchange of scientific information at expert group meetings and of continuing the programme of advisory services given by the Division of Narcotic Drugs to Member States through the preparation and provision of practical manuals. The Commission also recognized that such technical manuals permit further dissemination of scientific data as well as the harmonization of activities at the international level. It further encouraged the Division of Narcotic Drugs to serve as a focal point for various activities related to scientific and technical assistance.

Purpose of the Manual

In response to the Commission's request, a group of nine experts and one consultant was convened in September 1987 by the Division of Narcotic Drugs in Buenos Aires at the invitation of the Government of Argentina. The present manual published by the United Nations Division of Narcotic Drugs reflects the conclusions of the group of experts and has been designed to provide practical assistance to national authorities by

describing recommended methods to be used in forensic laboratories for the identification and analysis of illicit ring-substituted amphetamine derivatives. The manual may also serve as a guide to national authorities in assessing existing methods used within their own government and university laboratories.

This manual is one of a series of similar publications dealing with the identification and analysis of various groups of drugs under international control; it was preceded by manuals on heroin (ST/NAR/6), cocaine (ST/NAR/7), cannabis (ST/NAR/8) and amphetamine/methamphetamine (ST/NAR/9) analysis.

These manuals suggest approaches that may help the forensic analyst to select a technique appropriate to the sample currently being examined. The analyst may then choose to follow any of the methods described in the manual, as each method can be expected to produce reliable analytical information with respect to the samples to which they are applied. Each method has been used for a number of years in reputable forensic laboratories and has been published in the scientific literature. In identifying these methods, the expert group was aware that many other methods produce useful and acceptable information for the forensic analyst, and that a number of other acceptable options are recorded in the forensic scientific literature.

Use of the Manual

Few methods are perfect, least of all in forensic drug analysis where the materials under examination are very likely to show significant variation both in their physical form and chemical composition. The choice of methodology and approach to analysis remains within the control of the analyst working within his or her own country. The analyst alone has seen the suspect material and can best judge the correct approach to the problem at hand. Furthermore, the choice of methods may necessarily depend on the availability of reference materials and of instrumentation.

Not all methods listed need to be applied to all samples suspected to contain ring-substituted amphetamine derivatives. Requirements vary, for example, as a result of local trends in samples encountered, facilities available, and the standard of proof acceptable in the prosecution system within which the analyst works. The more complex methods are needed only for certain forensic requirements, such as comparison of samples or for source determination.

In order to establish the identity of any controlled drug, it is suggested that the criteria should be at least two independent analytical parameters. The selection of these parameters in any particular case would take into account the drug involved and the laboratory resources available to the analyst. For example, two uncorrelated TLC systems would count as two parameters. Uncorrelated TLC systems in this context means that either the solvent systems or the coating on the plates are completely different. When possible, three entirely different analytical techniques should be used, for example: colour test, chromatography (TLC, GLC or HPLC) and spectroscopy (IR or UV). The actual choice of parameters is left to the discretion of the chemist.

The ring-substituted amphetamines present a special problem to analysts in certain countries. Where a conclusive identification is required and there is evidence that other ring positional isomers are available in the illicit market in that country, more sophisticated techniques are necessary. The expert group felt that, for this reason, nuclear magnetic resonance (NMR) spectroscopy should be included in this manual. They recognize the expense and technical expertise required to operate this instrumentation and cautious that it should be used only in countries where the legal requirements and extent of the problem justify its use.

Attention is also drawn to the vital importance of the availability of textbooks on drugs of abuse and analytical techniques. Furthermore, the analyst must continually keep abreast of current trends in analysis, consistently following current analytical and forensic science literature. For this purpose, attention is drawn to the Multilingual Dictionary of Narcotic Drugs and Psychotropic Substances under International Control (ST/NAR/1), a vital tool for forensic laboratories, and to the Manual on Staff Skill Requirements and Basic Equipment for Narcotics Laboratories (ST/NAR/2), both published by the Division of Narcotic Drugs. The latter publication lists bibliographic references as well as a selection of well-known journals in the field. Analysts should refer to these and previous manuals in this series for general descriptions of the analytical techniques included in this manual.

Close liaison with national law enforcement and judicial authorities as well as between national narcotic laboratories and those at the regional level can lead to greater awareness of the latest trends in drug presentation, the illicit traffic, smuggling techniques and the preparation of evidence to courts of law. These in turn will produce a more meaningful choice of analytical techniques to be applied to the latest submissions.

It is equally important that the latest information on changes in drugs encountered in the illicit traffic be quickly disseminated. This may often need to be done prior to publication in specialized periodicals dealing with forensic and other chemical analyses, since these publications are available to the forensic community some two to three years after the changes become known. The value of frequently published national reports on the latest information on such changes in drugs and on work being undertaken and analytical results obtained within individual laboratories cannot be over-emphasized.

The Division of Narcotic Drugs would welcome observations on the contents and usefulness of the present manual. Comments and suggestions may be addressed to:

Division of Narcotic Drugs
United Nations Office at Vienna
Vienna International Centre
P.O. Box 500
A-1400 Vienna, Austria

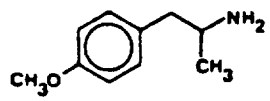
AMPHETAMINE-RELATED COMPOUNDS

I. DESCRIPTION OF THE PURE COMPOUNDS

4-METHOXYAMPHETAMINE

4-methoxy-α-methylbenzeneethanamine
p-methoxy-α-methylphenethylamine
PMA

Scheduled under the "Convention on Psychotropic Substances 1971"
4-methoxyamphetamine

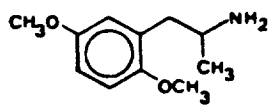


	base	hydrochloride
$C_{10}H_{15}NO$ M Wt. = 165.2	colourless oil	m.pt.= 208-209°C

2,5-DIMETHOXYAMPHETAMINE

2,5-dimethoxy-α-methylbenzeneethanamine
2,5-dimethoxy-α-methylphenethylamine
DMA

Scheduled under the "Convention on Psychotropic Substances 1971"
2,5-dimethoxyamphetamine

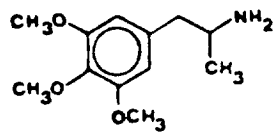


	base	hydrochloride
$C_{11}H_{17}NO_2$ M Wt. = 195.3	colourless oil	m.pt.=110-113°C

3,4,5-TRIMETHOXYAMPHETAMINE

3,4,5-trimethoxy-α-methylbenzeneethanamine
3,4,5-trimethoxy-α-methylphenethylamine
TMA

Scheduled under the "Convention on Psychotropic Substances 1971"
3,4,5-trimethoxyamphetamine

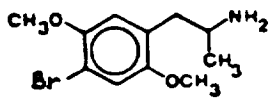


	base	hydrochloride
$C_{12}H_{19}NO_3$ M Wt. = 225.3	colourless oil	m.pt.= 219-220°C

4-BROMO-2,5-DIMETHOXYAMPHETAMINE

4-bromo-2,5-dimethoxy-α-methylbenzeneethanamine
4-bromo-2,5-dimethoxy-α-methylphenethylamine
DOB

Scheduled under the "Convention on Psychotropic Substances 1971"
2,5-dimethoxy-4-bromoamphetamine

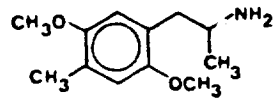


	base	hydrochloride
$C_{11}H_{16}BrNO_2$ M Wt. = 274.2	m.pt.=63-65°C	m.pt.=198-199°C

2,5-DIMETHOXY-4-METHYLAMPHETAMINE

2,5-dimethoxy-4,α-dimethylbenzeneethanamine
2,5-dimethoxy-4,α-dimethylphenethylamine
STP
DOM

Scheduled under the "Convention on Psychotropic Substances 1971"
2,5-dimethoxy-4-methylamphetamine

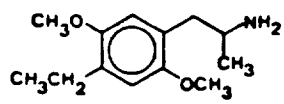


	base	hydrochloride
$C_{12}H_{19}NO_2$ M Wt. = 209.3	m.pt.=60.5-61°C	m.pt.=190-191°C

2,5-DIMETHOXY-4-ETHYLAMPHETAMINE

2,5-dimethoxy-4-ethyl-α-methylbenzeneethanamine
2,5-dimethoxy-4-ethyl-α-methylphenethylamine
DOET

Scheduled under the "Convention on Psychotropic Substances 1971"
2,5-dimethoxy-4-ethylamphetamine

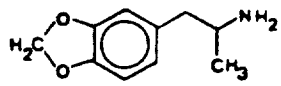


	base	hydrochloride
$C_{13}H_{21}NO_2$ M Wt. = 223.3	m.pt.=61-61.5°C	m.pt.= 195°C

3,4-METHYLENEDIOXYAMPHETAMINE

∝-methyl-1,3-benzodioxole-5-ethanamine
3,4-methylenedioxy-∝-methylphenethylamine
MDA

Scheduled under the "Convention on Psychotropic Substances 1971"
3,4-methylenedioxyamphetamine

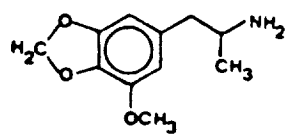


	base	hydrochloride
$C_{10}H_{13}NO_2$ M Wt. = 179.2	colourless oil	m.pt.=183-185°C

3-METHOXY-4,5-METHYLENEDIOXYAMPHETAMINE

7-methoxy-∝-methyl-1,3-benzodioxole-5-ethanamine
5-(∝-methyl)-ethanamine-7-methoxy-1,3-benzodioxole
MMDA

Scheduled under the "Convention on Psychotropic Substances 1971"
3-methoxy-4,5-methylenedioxyamphetamine

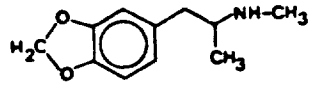


	base	hydrochloride
$C_{11}H_{15}NO_3$ M Wt. = 209.2	colourless oil	m.pt.=190-191°C

3,4-METHYLENEDIOXYMETHAMPHETAMINE

N,∝-dimethyl-1,3-benzodioxole-5-ethanamine
N,∝-dimethyl-3,4-methylenedioxyphenethylamine
5-(N,∝-dimethyl)-ethanamine-1,3,-benzodioxole
N-methyl-3,4-methylenedioxyamphetamine
MDMA

Scheduled under the "Convention on Psychotropic Substances 1971"
3,4-methylenedioxymethamphetamine



	base	hydrochloride
$C_{11}H_{15}NO_2$ M Wt. = 193.2	colourless oil	m.pt.=147-148°C

Solubilities

The free bases are generally insoluble in water and soluble in organic solvents such as ethanol, diethyl ether and chloroform.

The hydrochloride salts are soluble in water and ethanol, slightly soluble in chloroform and insoluble in diethyl ether.

II. PRODUCTION AND CHEMICAL CHARACTERISTICS OF RING-SUBSTITUTED AMPHETAMINE DERIVATIVES

None of the ring-substituted derivatives reviewed in this manual has been marketed as an approved drug. Although DMA is used in the photographic industry and some may be diverted from legitimate sources, the majority of these substances on the illicit market is produced by clandestine laboratories. The free bases, except for those of DOB, DOET and STP, are unstable colourless to brown oils. Virtually all of the illicit substances contain the drug in the form of the hydrochloride salt. They appear as powders, in tablets or capsules and, in the case of DOB, impregnated on paper (blotters).

STP was the first of these amphetamine-related substances to appear on the illicit market. Synthesized in 1963 for the first time, it appeared in 1967 in the USA as 10 mg tablets under the name STP, Serenity, Tranquility, Peace. It is 100 times more potent as a hallucinogen than mescaline. Because of its bad reputation, it has virtually passed from the street scene. It was scheduled under the Convention in 1977.

MDA was first synthesized in 1910 and explored in animal studies in 1939. It has been patented as an antitussive, ataractic and an anorexigenic. The R(-) isomer which is 3 times more active than the S(+) isomer has been chemically explored as an appetite suppressing drug and as an antidepressant; however, it has never been commercially available. Virtually all illicit MDA appear in the racemic form available as capsules containing 200-230 mg. MDA received widespread illicit use in the late 1960s and early 1970s when it was known as the Mellow Drug of America or the Love Drug. Although its popularity has tapered off since 1973 when several deaths were reported, it is still available in several countries. It was scheduled under the Convention in 1985.

DMA has no legitimate medicinal utility but has considerable demand as a chemical in the photographic industry. With a potency eight times that of mescaline, capsules of the drug appeared on the illicit market in 1970 in Canada and the USA. It was added to Schedule I of the Convention in 1986.

MMDA was synthesized in 1962 as one of a series of compounds to investigate the combined activity of mescaline and amphetamine. It is chemically similar to myristicin, the major component of nutmeg and mace. With an activity three times that of mescaline and an effective oral dose of 150 mg it was considered a very mild psychedelic drug. It was scheduled in Canada and the USA in 1970 and added to Schedule I of the Convention in 1986.

PMA first appeared in 1973 in Canada, then in the USA. With activity five times that of mescaline and an effective dose of 50 mg a number of deaths were reported. It as promptly scheduled in Canada and the USA in 1973 and included under the Convention in 1986.

TMA was first synthesized in 1947. Being a homolog of mescaline, its pharmacological activity was investigated in 1963, and it appeared on the illicit market in the early 1970s. Its activity is twice that of mescaline at an effective dose of 160-200 mg. TMA was scheduled in 1986.

DOB was reported in 1971 to be 200 times more potent than mescaline exhibiting full activity at doses of 0.8 - 2.0 mg. It appeared on the illicit market in the USA in 1972 and in Canada, Australia and in Europe in the late 1970s and early 1980s. In addition to tablets and powder forms, it has been sold impregnated on paper and other supporting media such as noodles. It was scheduled in 1985.

MDMA has recently reappeared in the illicit market under the names "ecstasy", "XCT" and "ADAM". It was originally reported in the patent literature in 1914, however, the first biological data were published only in 1973 on work conducted by the US Army in 1953-54. It was introduced as an underground drug in the late 1970s. To date it has no currently accepted medical use although some contend that it has enormous therapeutic potential in psychiatry and has been used as an adjunct in psychotherapy without approval. Clandestine syntheses of tablets, capsules and powders with an average dosage of 50-100 mg have been reported in North America and in Europe. It was listed as a Schedule I substance under the Convention in 1986.

DOET was patented as a stimulant in 1970 at the same time as STP. Its potency is 100 times that of mescaline with an effective dose of 1.5 to 4 mg. The R(-) enantiomer is four times as effective as the S(+) enantiomer. Chemicals for the clandestine manufacture of DOET were discovered recently in Canada for the first time. It was scheduled under the Convention in 1986.

Lack of quality control and variability in potency are characteristics of illicitly produced amphetamine-related substances. They often contain by-products and intermediates resulting from impure starting materials, incomplete reactions and inadequate purification of intermediates and the final synthetic product. These by-products and intermediates can provide valuable information concerning the illicit method of manufacture. Knowledge of the impurities is important for many reasons. The harmful effects of impurities can be evaluated, the potential danger publicized and treatment provided, if necessary. The presence or absence of specific impurities is useful in determining the synthetic route employed and in determining whether samples are from a common origin and/or from licit or illicit production. Awareness of the presence of particular impurities is important to the forensic analyst because of their potential interference in the analytical techniques employed for analysis of the exhibit.

The types and amounts of impurities present depend on the method of synthesis, the proportions and source of starting materials, the reaction time and temperature, the conditions of hydrolysis of intermediates and the purification procedures, if any, employed. Most impurities are weakly basic or neutral in nature and are normally present in the finished product at less than the 2-3% level.

Several different methods* have been used for the synthesis of these ring-substituted amphetamine compounds, the method of choice depending upon the ready availability of starting materials. The "Leuckart"

* Readers are referred to the previous amphetamine/methamphetamine manual in the series for a description of the chemistry involved in these synthetic procedures.

reaction has been popular, since the synthesis is simple, rapid, gives a good yield and does not involve any particularly hazardous procedure. For MDA, the phenylacetone intermediate is commercially available. The substituted benzaldehyde precursors of MDA, PMA, DMA, DOB, STP, DOET, TMA and MMDA are also commercially available. These serve as starting materials for the "nitrostyrene" method in which the benzaldehyde is condensed with nitroethane using n-butylamine or ammonium acetate. The resulting -nitrostyrene is then reduced using hydride transfer reagents such as $LiAlH_4$ or $NaBH_3CN$, or electron-transfer reagents such as sodium amalgam and sodium/ethanol.

Tetranitromethane has been employed for the preparation of the required nitrostyrenes when phenylpropene precursors such as myristicin for MMDA, isosafrole and safrole for MDA and elemicin for TMA were useed as the starting materials. Recently a new reagent, NO_2 generated in situ from $AgNO_2$/ $_2$, has been reported to produce the nitrostyrene from the styrenes in higher yields.

The bromine in DOB may be introduced by elemental bromination initially into the 2,5-dimethoxy benzaldehyde starting material or the final dimethoxyamphetamine stage.

The secondary amine MDMA has been prepared from the commercially available MDA phenylacetone precursor by reductive amination employing methylamine and $NaBH_3CN$ and by formylation or acylation of MDA followed by reduction with $LiAlH_4$.

All of the clandestine methods mentioned above produce the compounds as a racemic mixture. Optically pure enantiomers for most of these amphetamine-related substances have been prepared from the substituted P-2-P intermediate via in situ amine formation with optically active -methylbenzylamine, followed by reduction with Raney Nickel/hydrogen and crystallization of the resulting product. Catalytic N-debenzylation yields the pure optical isomer.

The purity of the uncut drugs on the street may range from 75-99%. For trafficking purposes they are usually cut to 40% or less with a carbohydrate (glucose, lactose, sucrose, mannitol), magnesium sulphate, caffeine, ephedrine, etc.

III. PHYSICAL APPEARANCE OF ILLICIT RING-SUBSTITUTED AMPHETAMINE DERIVATIVES

The illicit products vary in colour from a white to off-white powder, to yellow to brown depending upon the type and amount of impurities and adulterants. They are often damp with a characteristic unplesant odour owing to the presence of solvent residues. Many are trafficked in small gelatin capsules and as plain or mottled tablets. DOB is usually impregnated on paper similar to hits of LSD. In some countries the free base forms are trafficked as brown oils.

IV. THE ANALYSIS OF MATERIALS CONTAINING RING-SUBSTITUTED AMPHETAMINE DERIVATIVES

A. Sampling

The principal reason for a sampling procedure is to produce a correct and meaningful chemical analysis. Because most methods - qualitative and quantitative - used in forensic science laboratories for the examination of drugs require very small aliquots of material, it is vital that these small aliquots be entirely representative of the bulk from which they have been drawn. Sampling should be undertaken to conform to the principles of analytical chemistry, as laid down, for example, in national pharmacopoeias or by such organizations as the Association of Official Analytical Chemists.

There may be situations where, for legal reasons, the normal rules of sampling and homogenization cannot be followed, for example, if the analyst wishes to preserve some part of an exhibit as visual evidence. Alternatively, it may be necessary to perform separate assays on two powder items, rather than combining the powders prior to a single assay being performed on the mixture, because each has been separately exhibited by the seizing officer, and the legal system within which the analyst works requires individual results on every exhibit which is to be taken before the courts.

To preserve valuable resources and time, forensic analysts should seek, on all possible occasions, to use an approved sampling system and thereby reduce the number of quantitative determinations needed. To facilitate such an approach, the forensic analyst may need to discuss individual situations with both seizing officers and the legal personnel with whom he works.

Since none of these ring-substituted amphetamines has a currently accepted medicinal use, there is no legitimate commercial production and substances sold on the illicit market are produced by clandestine laboratories.

The free bases, except for those of DOB, DOET and STP are liquids and virtually all of the products are found in the form of their hydrochloride salt. They may be encountered as fine or gummy powders, tablets or capsules. DOB is usually absorbed onto paper or other substances and sold as tickets or blotters. Sheets are dipped into or sprayed with a solution of the drug. As the sheet dries, the drug migrates towards the edges, resulting in a concentration gradient across the sheet. The sheets are then cut up into 1 cm squares of varying dosage.

1. Powders

(a) Sampling of single package items

The simplest sampling situation is where the submitted item consists of a single package of material - in the case of the amphetamine-related substances, the material will most often be a powder. The material

should be removed from its container or wrappings, placed in a clean clear plastic bas and the net weight recorded. The material should be thoroughly homogenized prior to the application of the sequence of chemical tests, although presumptive testing may be applied at this stage if it is thought that the sampling or homogenization process will be lengthy and there is still some doubt as to the identity of the material. The simplest way to homogenize a powder is to shake it thoroughly within the clear plastic bag into which it has been transferred. If the powder contains aggregates these may be broken down by passing through successively finer sieves, or by pounding with a mortar and pestle, or by use of an adapted commercial food-mixer or food-processor.

Alternately, the technique of coning-and-quartering can be applied, as follows: the sample is mixed by shaking or stirring. Large fragments are reduced if necessary; the material is then poured onto a flat surface to form a cone. The "cone" is flattened and the material is then divided at right angles, forming quarters. Opposite quarters are taken for a sample, the remainder of the material is returned to the receptacle from which it was removed. Should further coning-and-quartering be desired to reduce sample size, particle sizes are further reduced, the material mixed thoroughly, poured onto a flat surface, and divided as before.

(b) Sampling of items consisting of more than one package

The analyst should examine the contents of all packages by eye, and possibly screen by using a simple colour test or TLC to determine:

1. If all packages contain suspect material, and/or

2. If one or more packages contain material different from that of the majority of packages. The simplest indicator is the physical appearance of the powder. If one or more packages obviously differ in content, these should be segregated and subjected to separate analysis.

The compositing of multiple container items is as follows:

(a) If there are less than 10 packages, all packages should be samples.

(b) If there are 10-100 packages, randomly select 10 packages.

(c) If there are more than 100 packages, randomly select a number of packages equal to the square root of the total number of packages rounded to the next higher integer.

If the powders are found to be the same then the contents of a number of packages may be combined; the combined bulk material may then be homogenized in, for example, an adapted commercial food-processor. Alternately, the bulk may be subjected to coning-and-quartering.

When different types of material have been identified in the various packages, then each sub-group should be composited in an identical fashion to that previously outlined.

Sampling errors for quantitative methods are reduced if large aliquots of material are subjected to sequential dilution with the dissolving solvent. If the total sample size is large, this approach may be adopted. However, when large amounts of material are used for the first dissolution, it may be necessary to add the solvents by pipette to avoid error due to insoluble materials. Insoluble adulterants are a frequent occurrence in "street" samples seized within all countries.

(c) Sampling of materials containing gummy or large aggregates

If the particles can be easily reduced to powder, then this approach should be used and sampling procedure followed as outlined previously. Powdering may be achieved by mortar and pestle, commercial food-processor/mixer, or industrial grinder. If the material cannot be easily broken down, then random sized particles should be drawn from at least three different parts of the item. A minimum of 1 gramme should be collected, weighed accurately and subjected to assay.

2. Blotters, Tablets and Capsules - Illicit Origin

For illicit preparations, quality control may be regarded as non-existent. Wide variations may be suspected in tablet make-up, although in most instances, some of the active constituent will be present in each tablet. Some screening of individual units or containers is, therefore, necessary.

(a) Single container

Determine the total number of dosage units and the average weight per dosage unit (du).

For sample sizes up to 10 du — screen all dosage units.

For sample sizes from 11 du to 27 du — randomly select and screen 3/4 of all dosage units, rounding upward to the next higher integer.

For sample sizes from 28 du — randomly select and screen 1/2 of all dosage units rounding upward to the next higher integer and selecting a minimum of 21 du and a maximum of 50 du.

Based on the results of the screening tests, proceed as follows:

1. If all dosage units appear to be identical, form a composite of screened dosage units as directed for licit preparations and analyze.

2. If the sample contains two dosage forms, subdivide the sample. If necessary, screen additional dosage units until both subsamples contain material for analysis, then form two composites and analyze.

3. If more than two dosage forms are present, the strategy is to make a composite of the most abundant dosage form, then to screen additional units until a sample of the same size is formed that contains only the less abundant dosage forms. This procedure if repeated until a composite is formed for each dosage form or until the sample is exhausted.

The percentage of dosage units containing a given controlled substance or other active constituent may be estimated by using the percent of units found to contain that substance out of the total number of units which were randomly selected and screened.

(b) Multiple containers

Randomly select a number of dosage units from each of a randomly selected number of containers. Screen each unit.

Based on the results of the screening test, proceed as follows:

1. If all screened units appear the same, combine screened units from all containers and form a composite.

2. If all screened units do not appear the same, each container should be treated as a separate exhibit or entity. Thus, for each container, proceed according to the direction above for a single container.

3. Aqueous Solutions - Illicit Origin

Aqueous solutions of some of these substances are illicitly available in some countries. Since solutions by their very nature are homogeneous, a relatively small sample (10 ml) represents the entire volume.

(a) Single containerr

If sample size permits, pipette an amount for assay of at least 10 ml.

(b) Multiple containers

Segregate containers by lot numbers or other characteristics and treat each group as described in 1.b above. Report results separately for each group.

Determine the square root of the total number of containers in each group. Randomly select a number of containers equivalent to the square root rounded to the next higher integer.

From each of the selected containers withdraw a 10 ml or larger sample (if size permits) for a composite.

If size permits, pipette at least 10 ml of the composite for assay.

4. Residues from Syringes or Clandestine Laboratory Glassware

Because of the trace amounts of drug usually present on hypodermic syringes seized from individuals or on glassware and other equipment found in clandestine laboratories, the analyst should not attempt to perform presumptive tests but should proceed directly with conclusive analytical procedures.

Wash the syringe or glassware with a minimum amount of methanol and concentrate it to dryness under a stream of nitrogen. Proceed with selected tests.

B. Presumptive tests

1. Colour tests

It must be stressed that positive results to colour tests are only presumptive indications of the possible presence of ring-substituted amphetamine derivatives. Many other materials, both ring-substituted amphetamines as well as those which are harmless and uncontrolled by national legislation or international treaties, may give similar colours with the test reagents. Some cutting agents may also result in the sample giving false positives or negatives. This is particularly true for the Simon's reagent. It is mandatory for analysts to confirm such results by the use of alternative techniques.

(a) Marquis' reagent

Prepare by adding 2-3 drops of 40% formaldehyde solution to 3 ml of concentrated sulphuric acid.

METHOD

Place a small amount of the sample (1-2 mg of powder; one or two drops if a liquid) in a depression of a spot plate, add the reagent dropwise (no more than three drops). The lower limit of detection is about 1 ug).

(b) Simon's reagent

Solution A. 2% aqueous sodium carbonate solution

Solution B. 10% (v/v) acetaldehyde is added to 1% aqueous solution of sodium nitroprusside.

METHOD

Place a small amount of the sample on a spotting tile and mix it with a drop of solution A. Then add 2 drops of solution B. This test may be used to distinguish between primary and secondary amines. Note, however, that the presence of some cutting agents may result in a false negative.

(c) Gallic acid reagent

Dissolve 0.1 g gallic acid in 20 ml concentrated sulphuric acid.

METHOD

Place a small amount of the sample (1-2 mg of powder) in a small test tube. Add one drop of the reagent solution. This test may be used to identify substances containing the methylenedioxy ring substituent. MDA, MMDA and MDMA give a bright to dark green colour.

RESULTS

Colour Tests for Ring-Substituted Amphetamine-Derivatives

COMPOUND	MARQUIS' REAGENT	SIMON'S REAGENT
amphetamine	bright orange — brown	brown/NR
PMA	NR — light green	light pink*
DMA	green — dark green	dull pink*
DOB	yellow green — green	light pink*
DOET	yellow brown	light pink*
STP	yellow	light pink*
MDA	black	light pink*
TMA	orange red	light pink*
MMDA	purple	light pink*
MDMA	black	deep blue
methamphetamine	orange/red brown	deep blue

NR = no reaction
* = colour of the reagent, should be considered as negative

C. Thin layer chromatography

PLATES

Activated silica gel G on glass backed plates; the coating (0.25 mm thickness) contain a fluorescing additive which fluoresces at 254 nm.

DEVELOPING SOLVENTS

SYSTEM A:	Methanol	100
	Concentrated ammonia	1.5
SYSTEM B:	Ethylacetate	85
	Methanol	10
	Concentrated ammonia	5

Preparation of solutions to be applied to the TLC plates

Powder: Prepare a solution at a concentration of 5 mg per ml in methanol.

Capsules: Remove the contents of a representative sample of capsules (see sampling procedure above) and prepare a solution containing the equivalent of approximately 5 mg of the drug per ml in methanol.

Tablets: Grind a representative number of tablets to a fine powder and prepare a solution containing the equivalent of approximately 5 mg of the drug per ml in methanol.

Blotters: Place a representative number of squares in sufficient methanol to give a solution containing approximately 5 mg of drug per ml. Sonicate the solution for 20 minutes before spotting.

Aqueous solutions: Spot directly or the equivalent of 5 mg/ml if the concentration of the drug is known.

Standard solutions: All made at a concentration of 5 mg per ml in methanol.

Apply 1 ul of a 5 mg per ml solution of the drug in methanol to the plate.

In those cases where it is suspected that the concentration of the drug in the sample is very low due to adulteration etc., it may be necessary to prepare a ten-times more concentrated solution for the analysis.

The form of standards and exhibits used, salt or base, is unimportant. Either form will be satisfactory. Because of the basic nature of the developing solvents the compounds chromatograph as the free bases.

VISUALIZATION

The plates must be dried prior to visualization. This can be done at 120°C for 10 minutes in an oven, or more quickly, by use of a hot air blower. It is important for proper colour development, however, that all traces of ammonia be removed from the plate.

Visualization methods

(a) Ninhydrin reagent

Prepare a 10% solution in ethanol

METHOD

Spray with the ninhydrin reagent and heat in an oven at 120°C for at least 15 minutes. Violet or pink spots are given by primary amines such as amphetamine and more intense spots for secondary amines such as MDMA.

(b) Fast Black K reagent

Solution A: 1% Fast Black K salt in water.

Solution B: 1N NaOH

METHOD

Spray the plates with solution A and observe any coloured spots. Secondary amines such as MDMA produce spots immediately - overspraying with solution B produces coloured spots for the other ring-substituted amphetamines. Air dry the plates and spray once more with solution A. This produces more intensely coloured spots. The colours vary from violet for primary amines to orange for secondary amines such as methamphetamine and MDMA.

RESULTS

TLC Rf x 100 values

COMPOUND	DEVELOPING SOLVENT	
	A	B
AMP	44	66
PMA	41	62
DMA	37	65
DOB	37	62
DOET	36	61
STP	35	63
MDA	41	62
TMA	35	48
MMDA	40	61
MDMA	31	62
METH	33	63

D. Gas liquid chromatography

1. Packed column techniques

Operating conditions:

Detector:	FID
Column:	6 ft (or 2 m), 2 to 4 mm ID glass
Packing:	3% SE-30 or OV-1 on 80-100 mesh Chromosorb W HP
Carrier gas:	Nitrogen at 30 ml per minute
Column temperature:	Programmed from 130^{O} to 260^{O}C
Internal standard:	n-Tetradecane or other n-alkanes

METHOD

Solutions of the standard (1 mg base/ml) are prepared by dissolving an accurately weighed portion of the salt in water. Make the solution alkaline by the addition of a few drops of 1.0N NaOH. Add an equal volume of the extracting solvent (hexane or ethylacetate), shake and allow the layers to separate. Dry the organic layer over anhydrous $MgSO_4$. The final concentration should be about 1 mg of base and 1 mg of internal standard per ml.

Treat the illicit sample in a similar manner using sufficient sample to give a drug concentration approximately equal to that of the standard solution.

Inject 1 to 2 ul of the organic layer as appropriate.

For quantitation, include the internal standard in the ethylacetate extracting solvent.

NOTE: Analysts should be aware that the peak shapes of ring-substituted amphetamines and the resolving power of packed column technology does not make gas chromatography a reliable method for quantitative analysis.

The content (%) of any component can be calculated using the general formula:

$$C_x\% = \frac{C_{r.\ std.}}{C_{sam.}} \times \frac{A_x / A_{int.std.in\ sam.\ chrom.}}{A_{r.st.} / A_{int.std.in\ std.\ chrom.}} \times 100$$

Where:

$C_x\%$ = content of component x in the sample (w/w %)

$C_{r.std.}$ = concentration of substance x in the standard reference soltuion (w/v %)

$C_{sam.}$ = concentration of the sample (w/v %)

A_x = peak area for substance x obtained during the sample chromatography

$A_{r.\ std.}$ = peak area for substance x obtained during the standard chromatography

$A_{int.\ std.\ in\ sam.\ chrom.}$ = peak area of the internal standard obtained during the sample chromatography

$A_{int.\ std.\ in\ std.\ chrom.}$ = area of the internal standard obtained during the standard chromatography

2. Capillary column technique

Operating conditions:

Detector	FID
Column:	Fused silica, chemically bonded and cross-linked methyl silicone or methyl phenylsilicone, such as SE-54, DB-1, DB-5 or equivalent
Film thickness:	0.25 um
Length:	10 to 30 m, ID 0.25 mm
Carrier gas:	Helium, 40 cm/sec.
Split ratio:	40:1
Column temperature:	Programme: 2 min. at 75°C, increase to 280°C at 10°/min.
Internal standard:	n-Tetradecane or other n-alkanes

METHOD

Prepare drug standard solutions and unknown sample solutions at a concentration of 1 mg of the free base per 1 ml H_2O as described above for the packed column method.

RESULTS

ELUTION PROFILES ON SELECTED COLUMNS (Retention indices)

COMPOUND	OV-1 or SE-30	DB-1 Capillary
AMP	1123	1095 (2.13 min.)*
PMA	1412	1346
DMA	1558	1527
DOB	1809	1786 (9.62 min.)
DOET	1654	1654
STP	1618	1593
MDA	1477	1444
TMA	1739	1684
MMDA	1705	1666
MDMA	1585	1501
METH	1176	1164

* Retention time

C. High Performance Liquid Chromatography

1. Isocratic technique

(a) Normal phase

Column:	125 mm by 4.9 mm ID.
Packing material:	Silica HPLC grade, 5 um diameter (Spherisorb S5W or equivalent).
Mobile phase:	Methanol: aqueous ammonium nitrate buffer solution (90:10 v/v). To prepare the 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.
Detection:	UV at 254 nm.
Sample preparation:	All materials are dissolved in methanol to give an approximate concentration of 1 mg free base per ml.
Standard solution:	Dissolve a sufficient amount of drug standard to give a solution containing 1 mg free base per 1 ml of methanol.
Injection volume:	1 to 5 ml by syringe or loop injector.
Quantitations:	By peak areas, external standard method.

(b) Reverse phase

Column:	250 mm by 4 mm ID.
Packing material:	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 addition of ammonia or acetic acid.
Flow rate:	1.5 ml per minute.
Temperature:	35°C
Detector:	UV at 254 nm
Sample preparation:	All materials are dissolved in a mixture of 2 parts water and 1 part acetonitrile to give an approximate concentration of 2-6 mg per ml.
Injection volume:	10-20 ul by loop injector.
Quantitation:	By peak areas, internal standard method using lidocaine or procaine or external standard method.

RESULTS

The capacitance ratios (K' values) or retention times (in minutes) are as follows:

COMPOUND	NORMAL PHASE	REVERSE PHASE
AMP	0.46 (2.77 min.)	5.24 (9.9 min.)
PMA	0.57	4.61
DMA	0.54	4.61
DOB	0.58	10.36
DOET	0.51	15.52
STP	0.53	9.16
MDA	1.23	3.84
TMA	0.77	2.73
MMDA	0.53	3.60
MDMA	1.17	8.09
METH	1.14	11.41

F. Other techniques

1. Infrared spectroscopy

Theoretically each substance has a unique infrared spectrum and this method would permit the unequivocable identification of all amphetamine derivatives. With illicit samples, however, a prior separation and isolation of the drug in a pure form free from diluents and adulterants is essential for the conclusive identification of closely related ring-substituted compounds. This may be achieved by column or preparative thin-layer chromatography, acid/base extraction or by the direct (dry) extraction method.

Isolation of pure drug from sample

a) For isolation of the amphetamine free base:

Dissolve 25-50 mg of the sample in 1 ml of 0.1 N tartaric acid. Add 4-5 drops ammonium hydroxide and extract with $CHCl_3$. Pass the $CHCl_3$ layer through a small column containing a cotton pledget and celite to remove suspended particles. Allow a portion of the $CHCl_3$ solution to evaporate directly onto a KBr disk and record the infrared spectrum of the free base by the thin film technique on KBr disks.

b) For isolation of the amphetamine salt:

Triturate a 20-50 mg portion of the sample with 1-2 ml of $CHCl_3$. Filter, collect the extract and evaporate to dryness. Induce crystallization and run the infrared spectrum of the resulting amphetamine salt by the KBr disk method.

METHOD

For a description of the standard method (halide disk, microhalide, nujol mull and thin film techniques) see previous manuals in this series. Both the free bases and salts can be used for the identification. Since even the salts tend to be hygroscopic, considerable difficulty may frequently be encountered in obtaining a KBr disk suitable for use.

RESULTS

In general, spectra of the hydrochloride salts of the ring-substituted amphetamine derivatives are recorded using samples prepared by the halide disk method and the free bases, which are oily liquids, are run as thin films. The free bases of DOB, DOET and STP are powders and have been run by the halide disk method.

Significant absorption bands, to aid in identification, are listed on the attached spectra of the pure reference substances. The intensities, however, may vary from sample to sample.

2. ^{1}H nuclear magnetic resonance (NMR) spectroscopy

Because of the ready availability of starting materials and the ease of synthesis, a wide variety of ring-positional isomers of these amphetamine derivatives has been encountered in certain countries. Their correct analysis and conclusive identification is a highly complex task even for the best equipped laboratories. NMR enables the analyst to unequivocably distinguish between particular ring-substituted amphetamine derivatives even in the presence of diluents and other adulterants. Although certain substitution patterns resemble one another in the area corresponding to the protons of the alkyl side chain, the integrated spectrum and the pattern of the aromatic proton signals allow their distinction from one another. Because of the cost and technical expertise required, NMR is not recommended for routine sample analysis. NMR will be required only in those laboratories where significant numbers of samples and the legal requirements of the country justify the expense.

METHOD

Dissolve about 20 mg of the drug sample in 1 ml of D_2O. If insoluble materials are present, centrifuge, otherwise transfer directly the supernatant into an NMR tube. Record the spectrum of this solution containing the hydrochloride salt of the amphetamine derivative.

Liberate the free base of the amphetamine *in situ* by the addition of 20-30 mg solid K_2CO_3 and 0.5 ml of $CDCl_3$ and record the spectrum of the free base. Compare the spectrum of the unknown with the reference spectra which were recorded on a Fourier transform instrument at 80 MHz using a flip angle of 18° (1 usec) with no delay following data acquisition.

For further information on ^{1}H-NMR or ^{13}C-NMR techniques for ring-substituted amphetamine derivatives, readers are referred to:

1. J.A.O.A.C. 57 (1974) pp 70-78.

2. J.A.O.A.C. 59 (1976) pp 1162-1169.

3. J. Pharm. Sci. 65 (1976) pp 412-417.

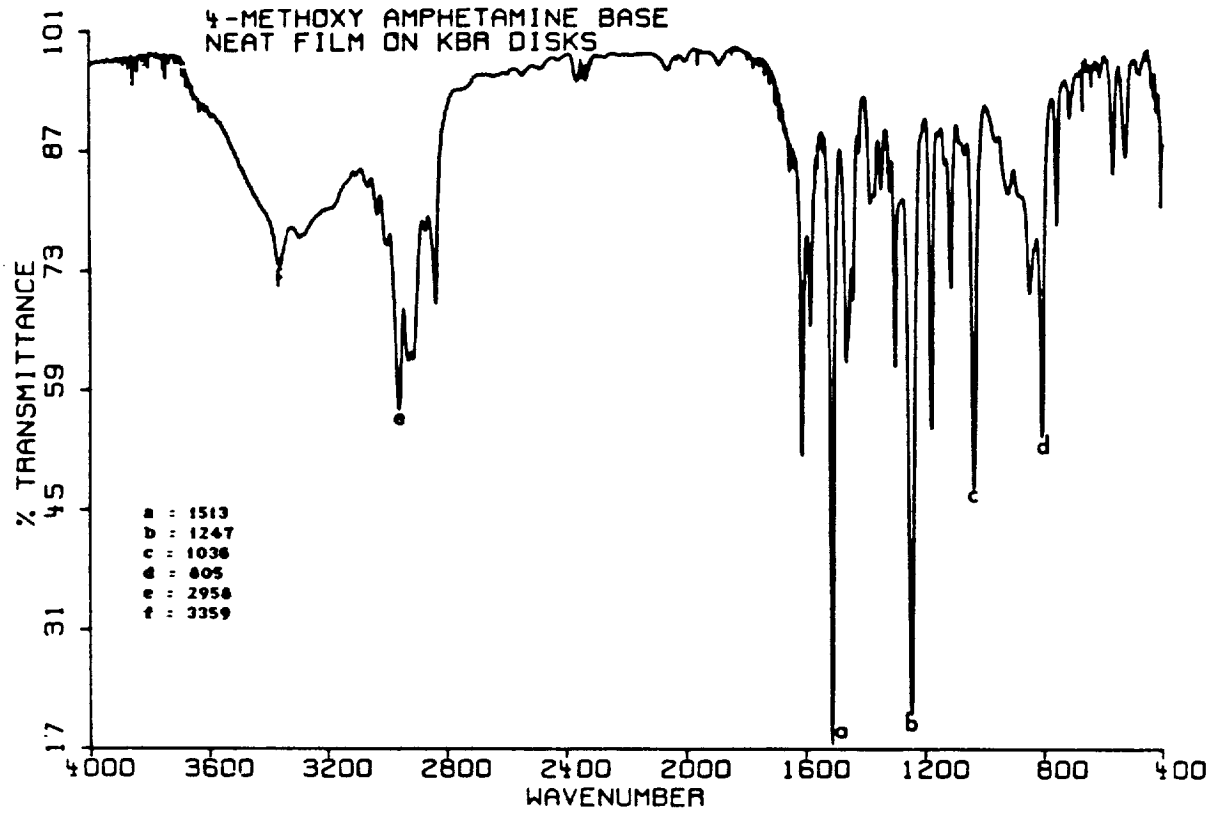
4. J. Forensic Sci. 26 (1981) pp 27-34.

5. Org. Mag. Resonance 21 (1983) pp 391-396.

6. J. Forensic Sci. 28 (1983) pp 386-390.

7. Applied Spect. 39 (1985) pp 604-610.

8. J. Pharm. Biomed. Analysis 5 (1987) pp 119-129.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87
73
59
45
31
17
a : 1513
b : 1247
c : 1036
d : 805
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f : 3359
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2400
2000
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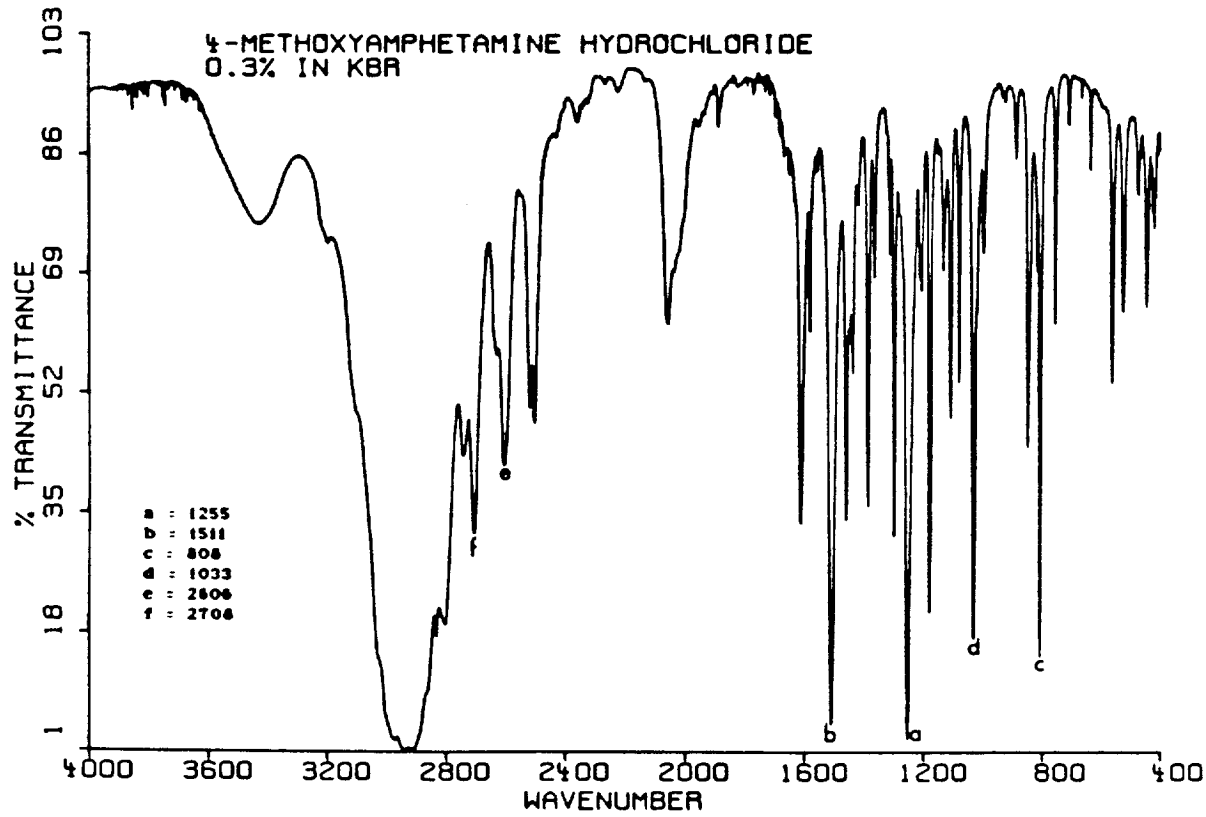
800
400
WAVENUMBER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0.3% IN KBR
% TRANSMITTANCE
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86
69
52
35
18
1
a : 1255
b : 1511
c : 808
d : 1033
e : 2606
f : 2706
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3200
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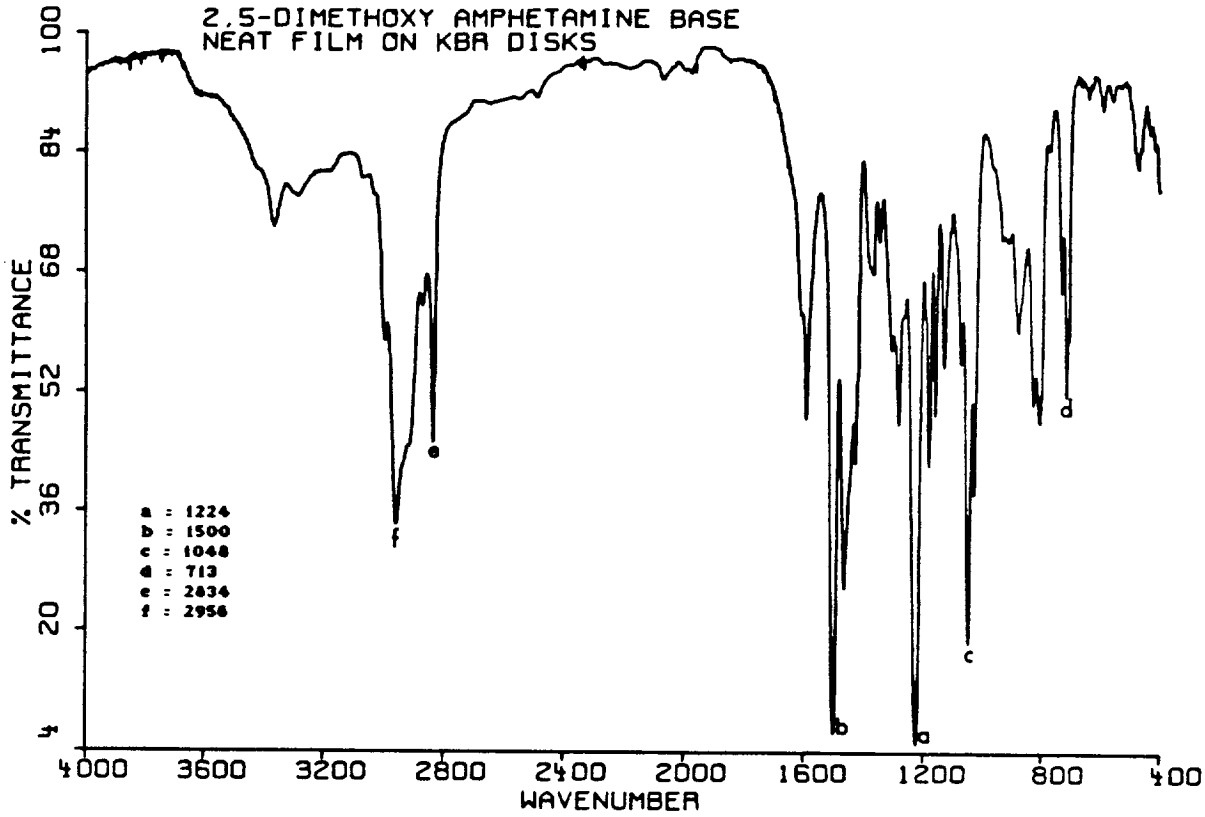
2400
2000
1600
1200
800
400
WAVENUMBER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NEAT FILM ON KBR DISKS
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68
52
36
20
4
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b : 1500
c : 1048
d : 713
e : 2834
f : 2956
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800
400
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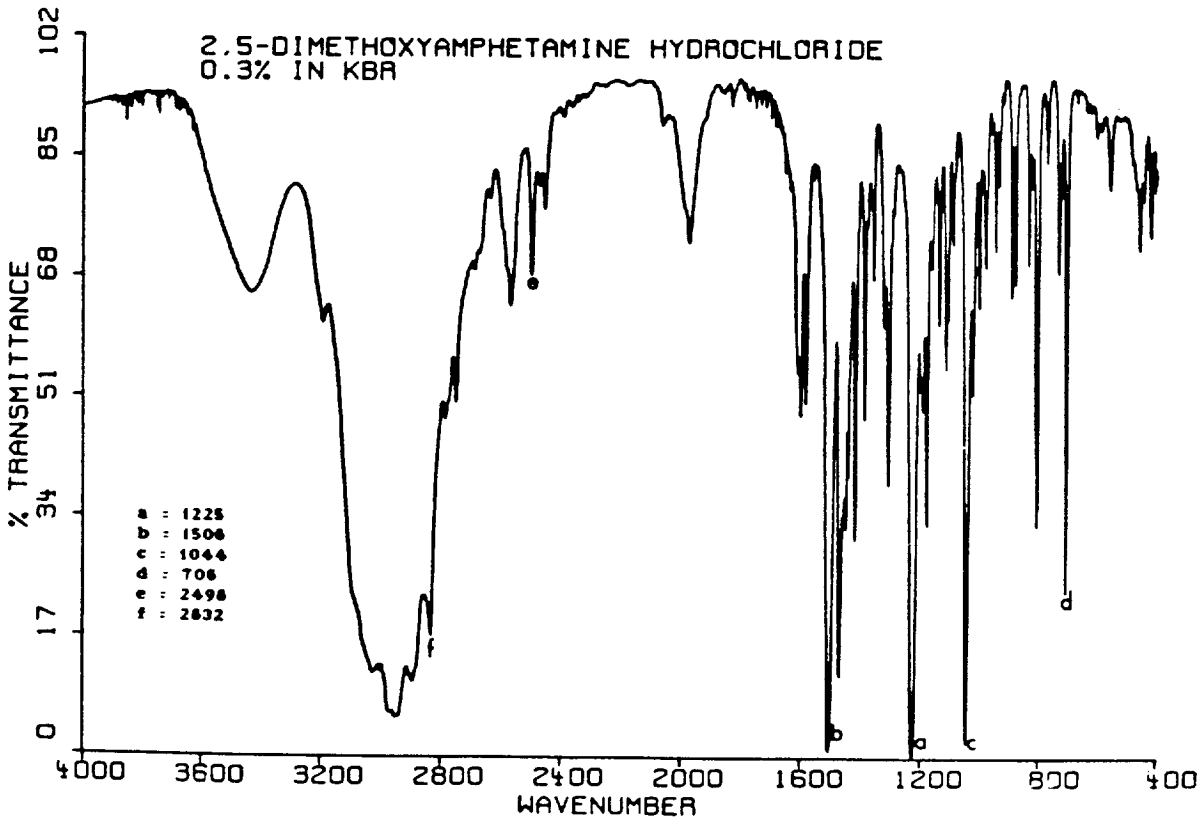
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% TRANSMITTANCE
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68
51
34
17
0
a : 1225
b : 1506
c : 1044
d : 706
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f : 2832
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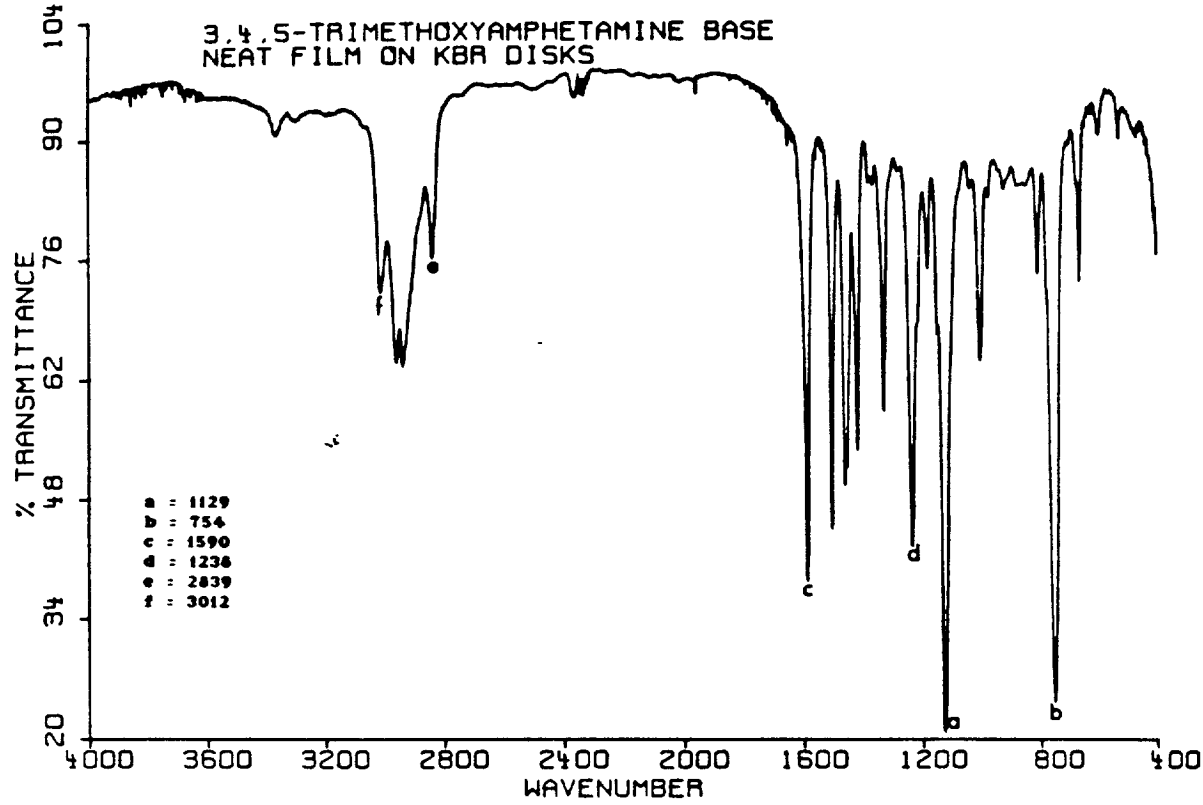
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NEAT FILM ON KBR DISKS
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62
48
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20
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b = 754
c = 1590
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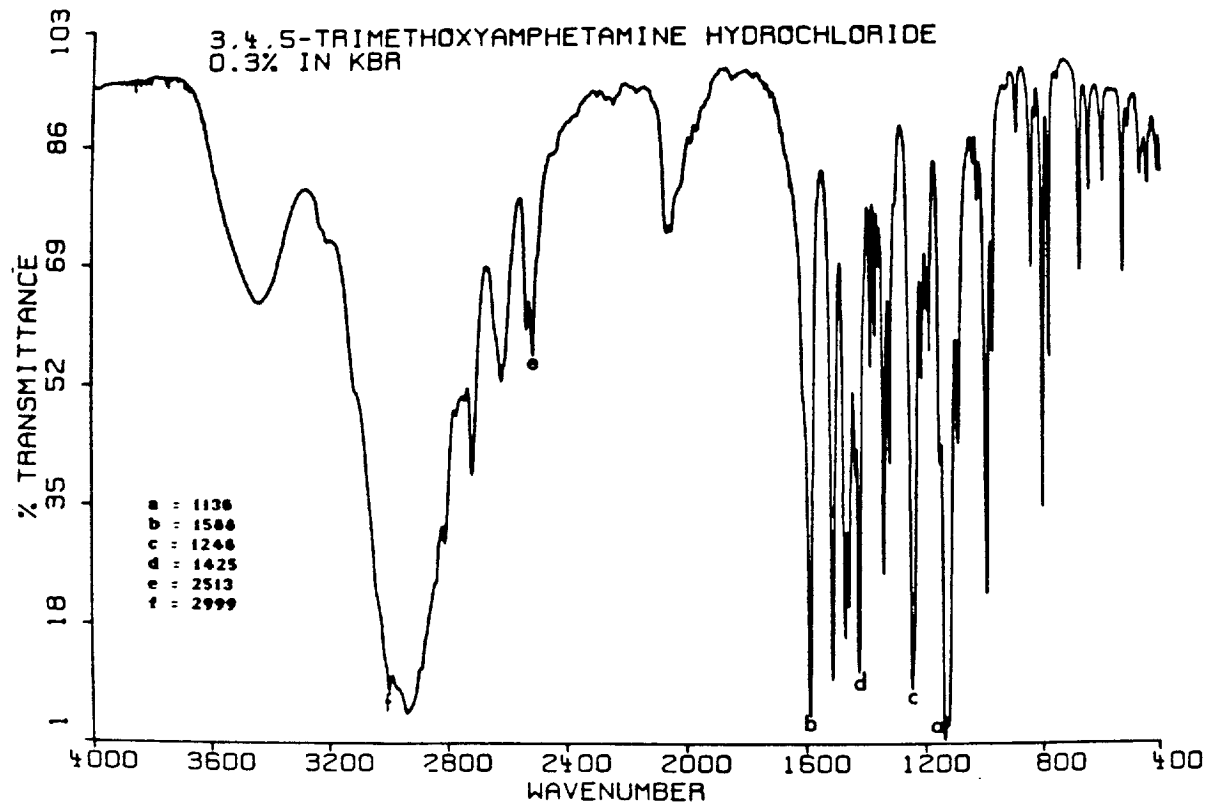
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% TRANSMITTANCE
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69
52
35
18
1
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b = 1588
c = 1246
d = 1425
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1200
800
400
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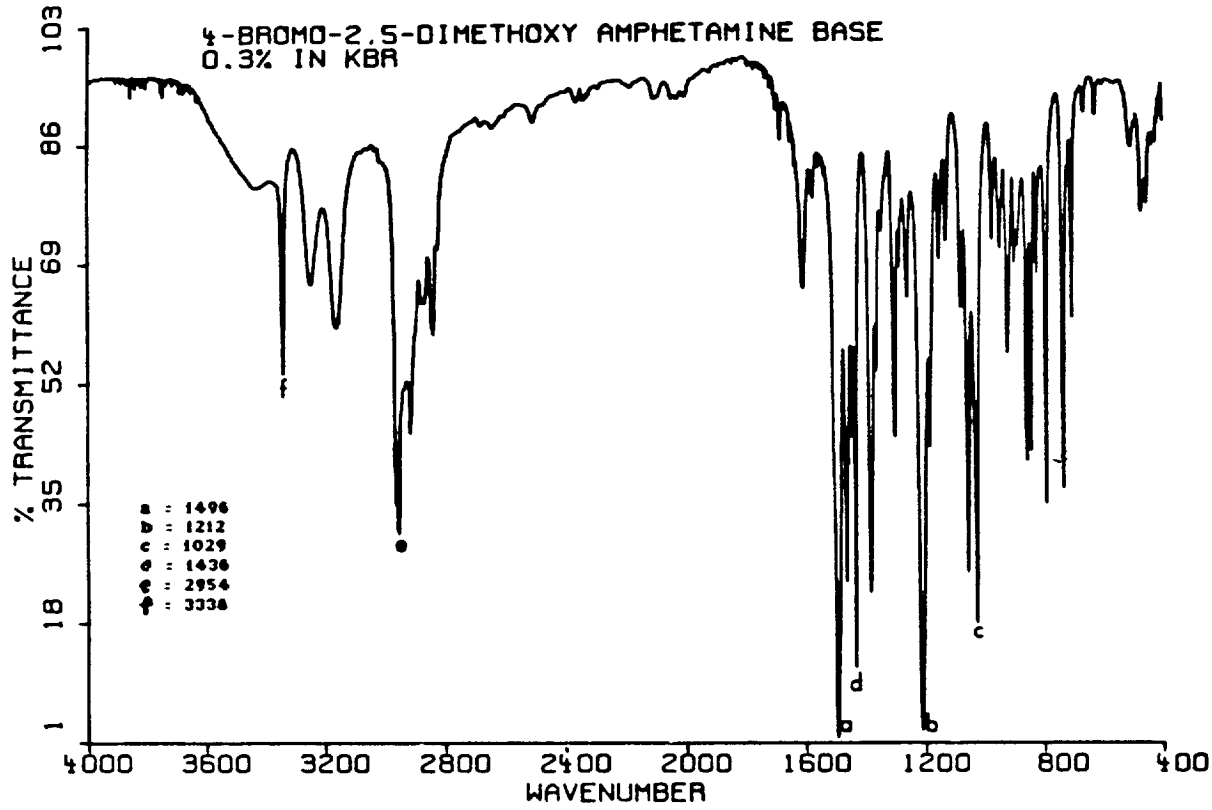
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% TRANSMITTANCE
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52
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b = 1212
c = 1029
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400
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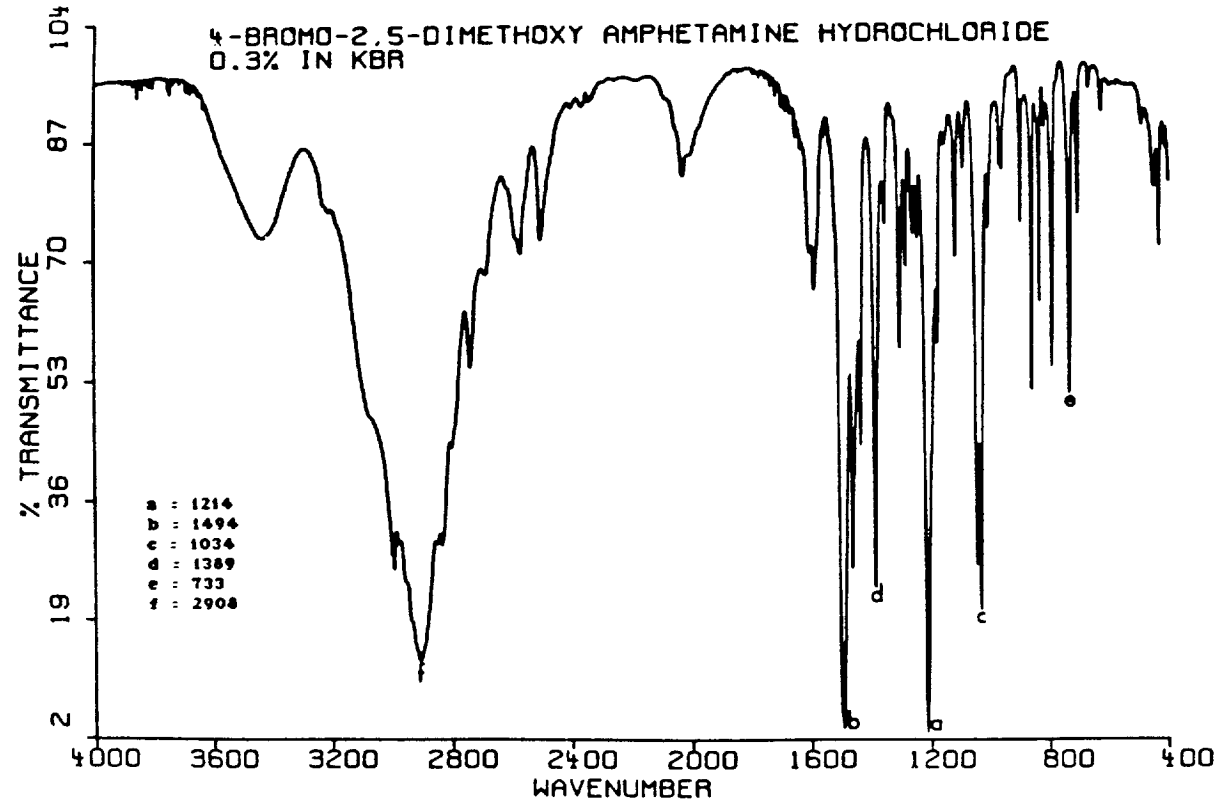
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% TRANSMITTANCE
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70
53
36
19
2
a = 1214
b = 1494
c = 1034
d = 1389
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1200
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400
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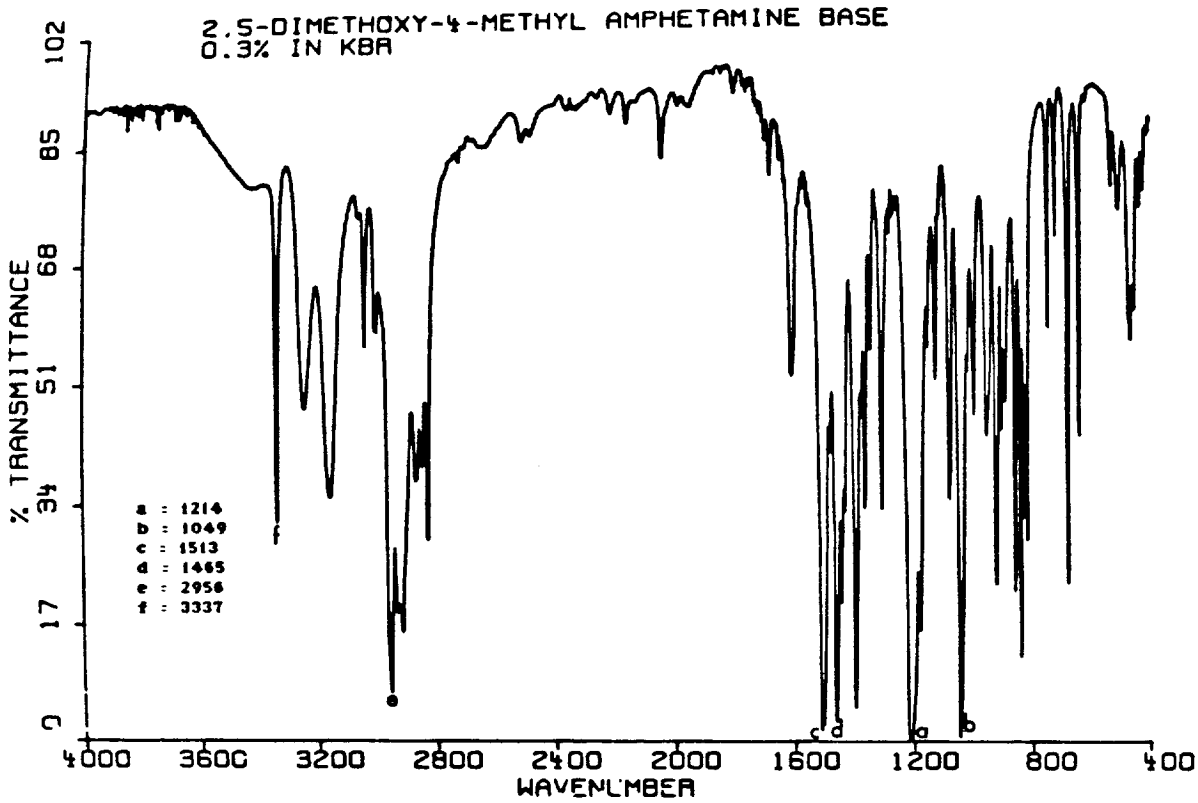
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% TRANSMITTANCE
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68
51
34
17
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a : 1214
b : 1049
c : 1513
d : 1465
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f : 3337
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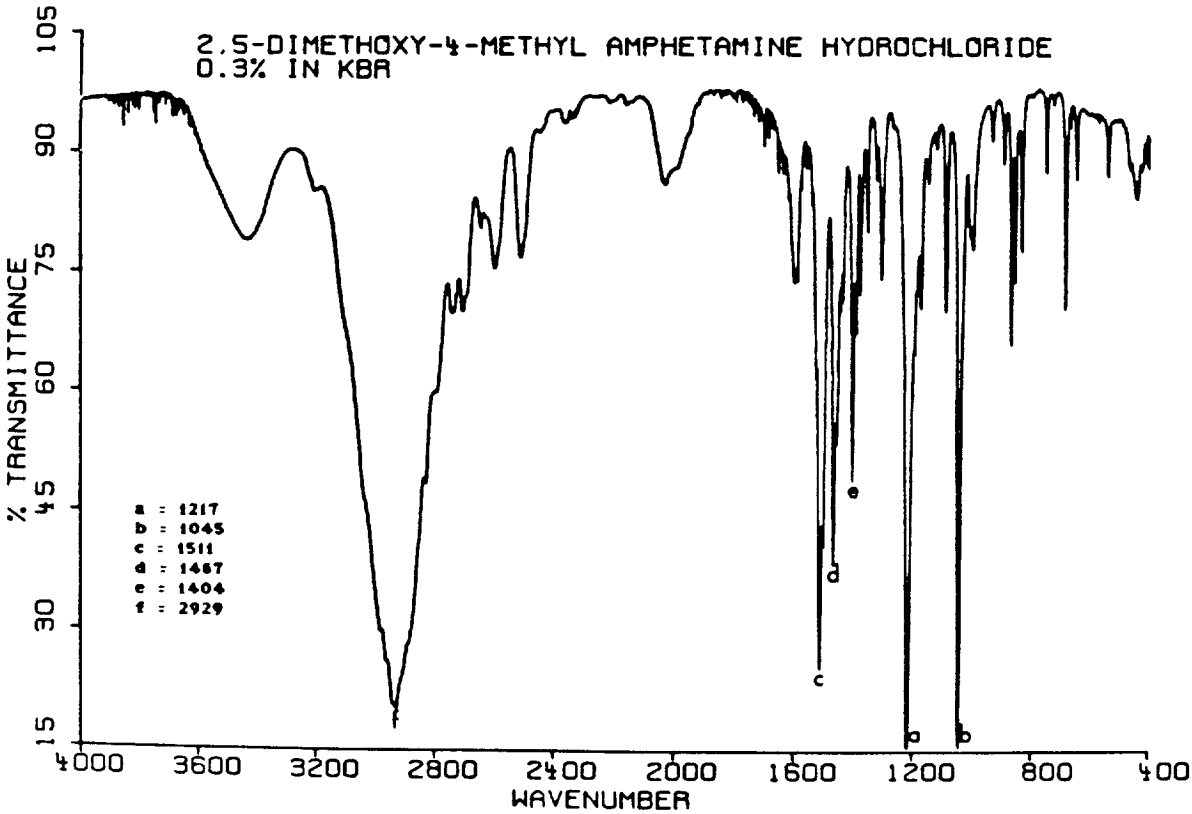
2400
2000
1600
1200
800
400
WAVENUMBER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% TRANSMITTANCE
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90
75
60
45
30
15
a : 1217
b : 1045
c : 1511
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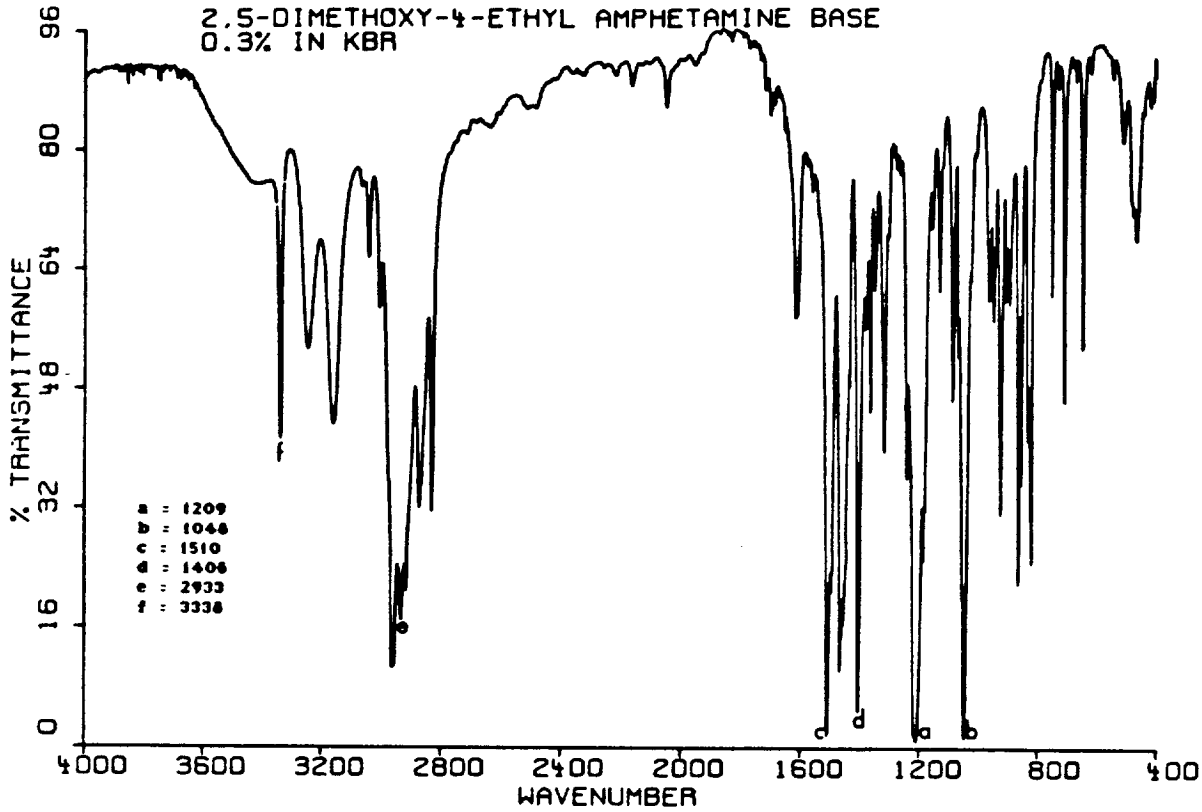
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% TRANSMITTANCE
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96
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b = 1048
c = 1510
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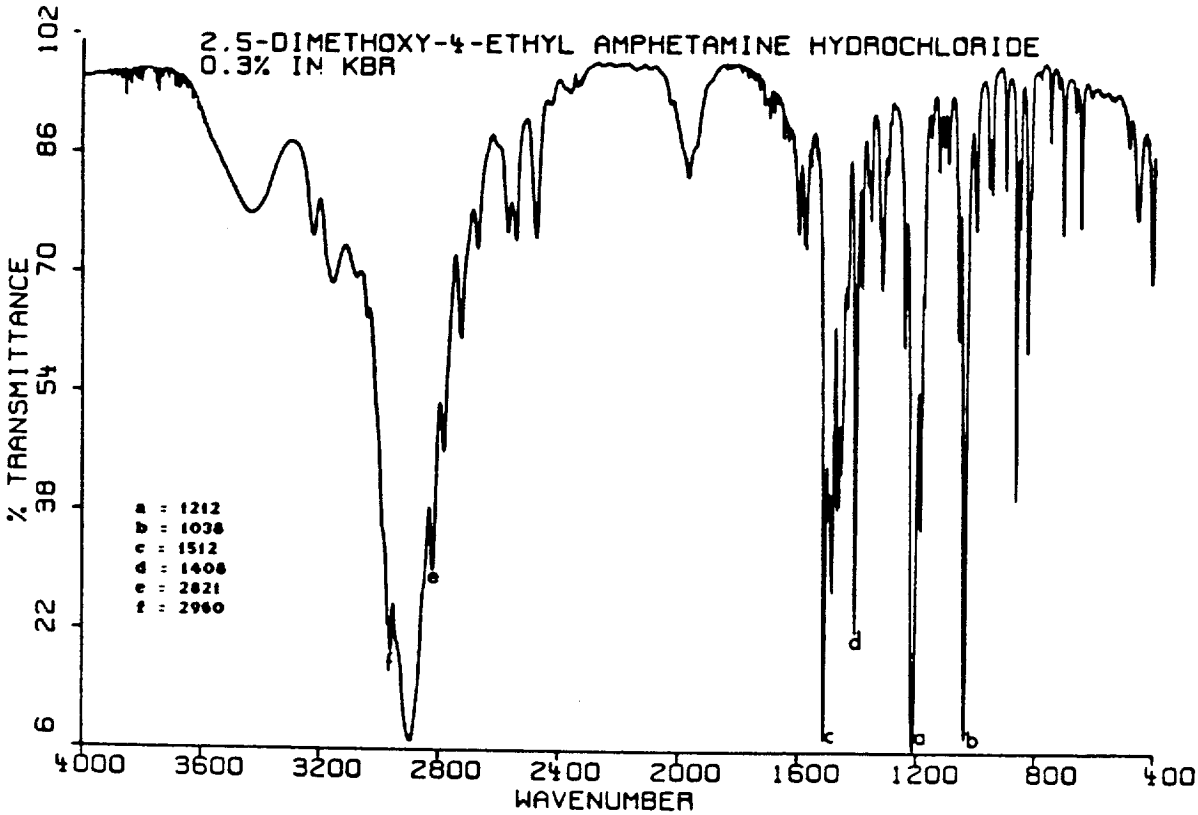
400
WAVENUMBER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% TRANSMITTANCE
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22
38
54
70
86
102
a = 1212
b = 1038
c = 1512
d = 1408
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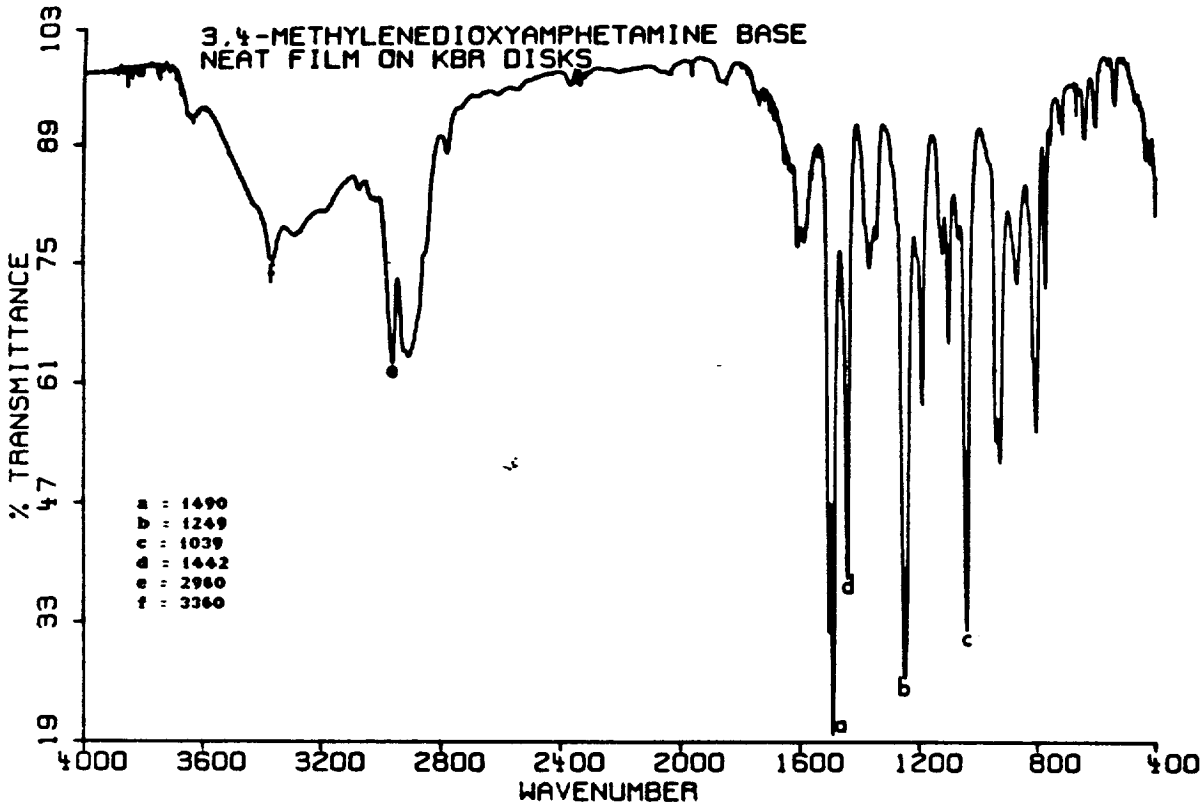
WAVENUMBER


3,4-METHYLENEDIOXYAMPHETAMINE BASE
NEAT FILM ON KBR DISKS
% TRANSMITTANCE
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89
75
61
47
33
19
a : 1490
b : 1249
c : 1039
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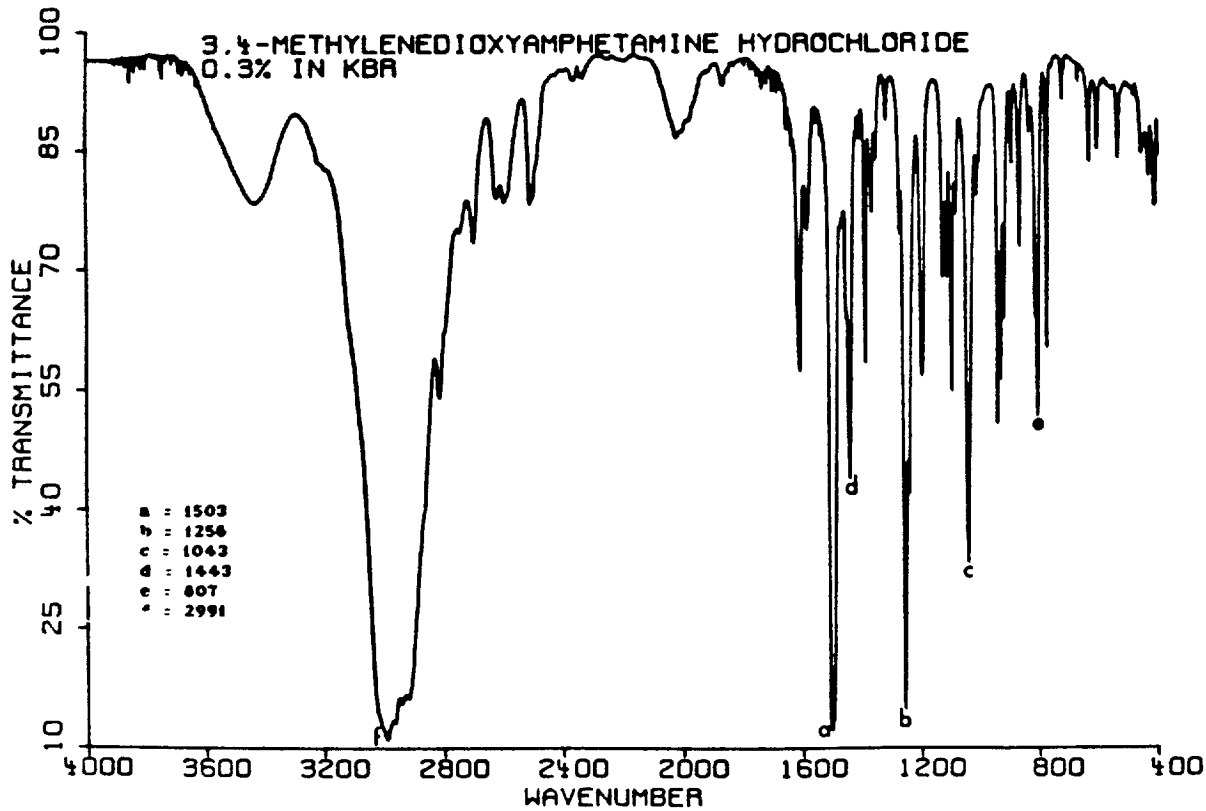
WAVENUMBER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0.3% IN KBR
% TRANSMITTANCE
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70
55
40
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10
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b : 1256
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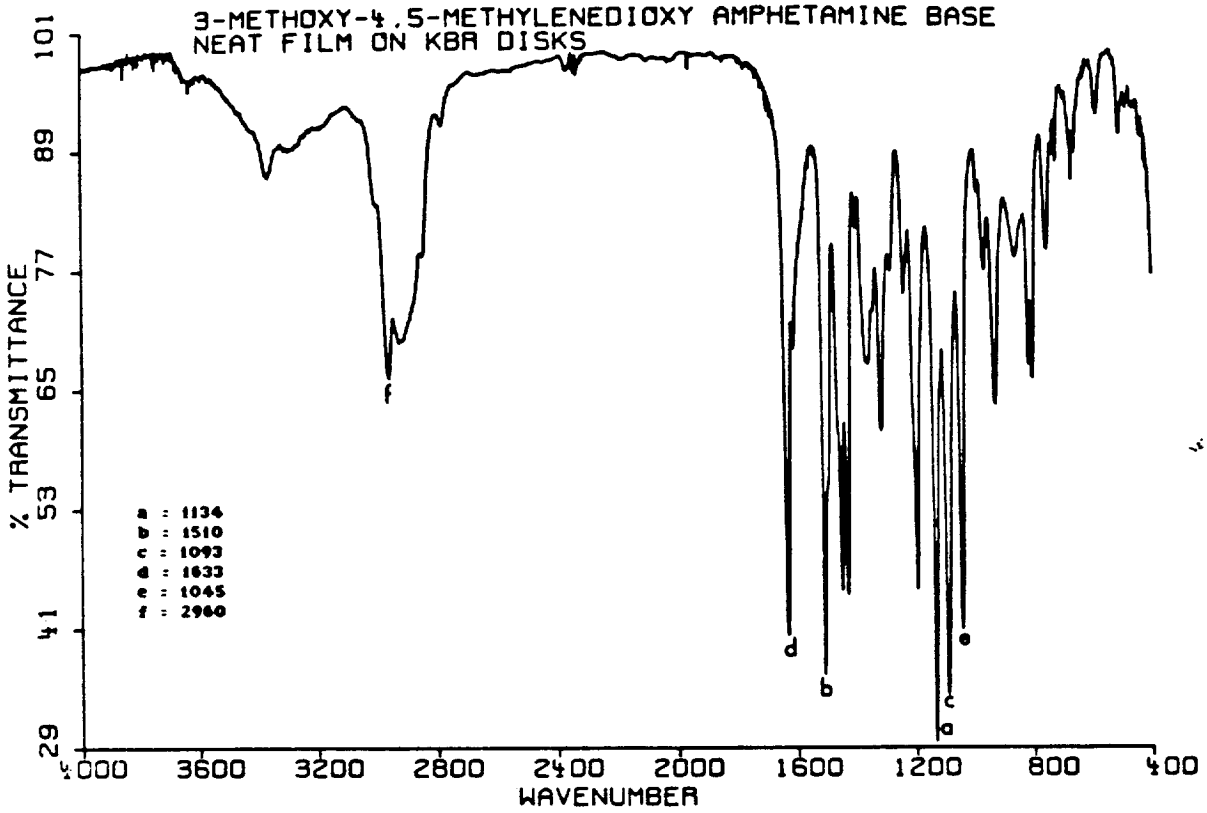
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NEAT FILM ON KBR DISKS
% TRANSMITTANCE
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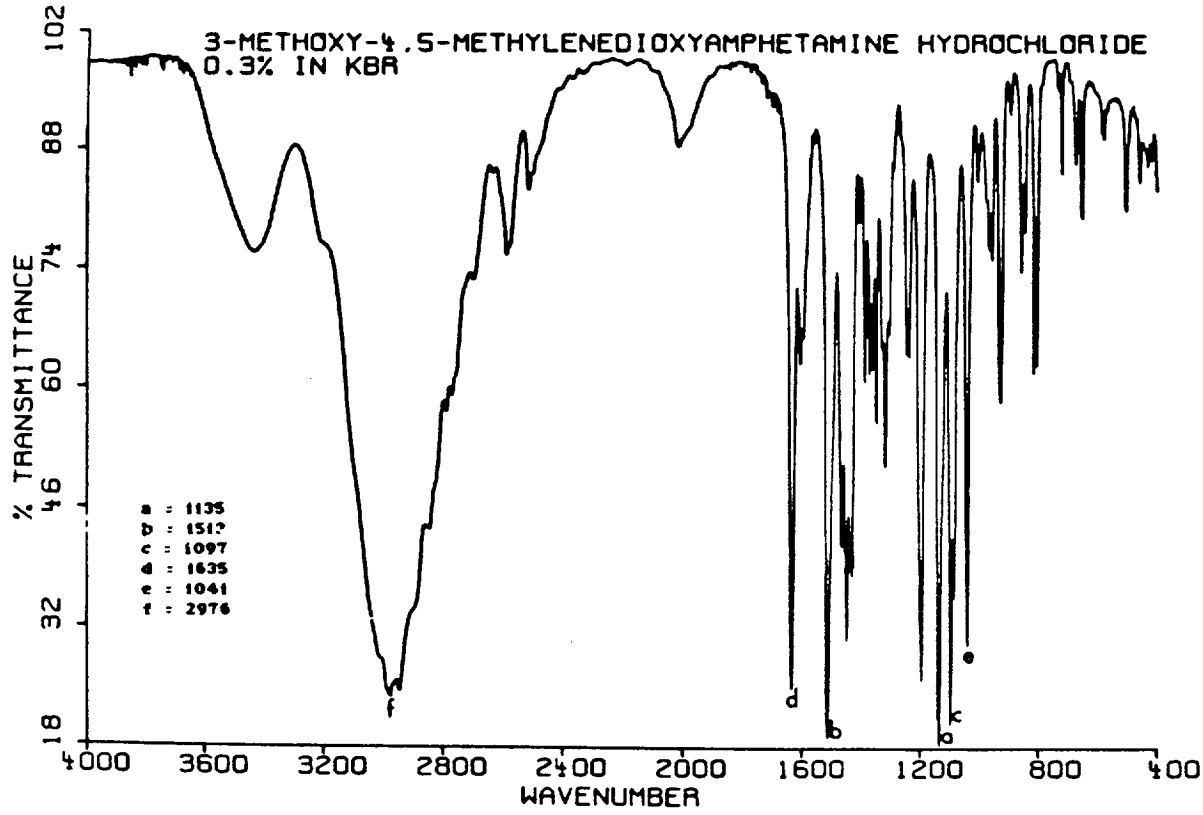
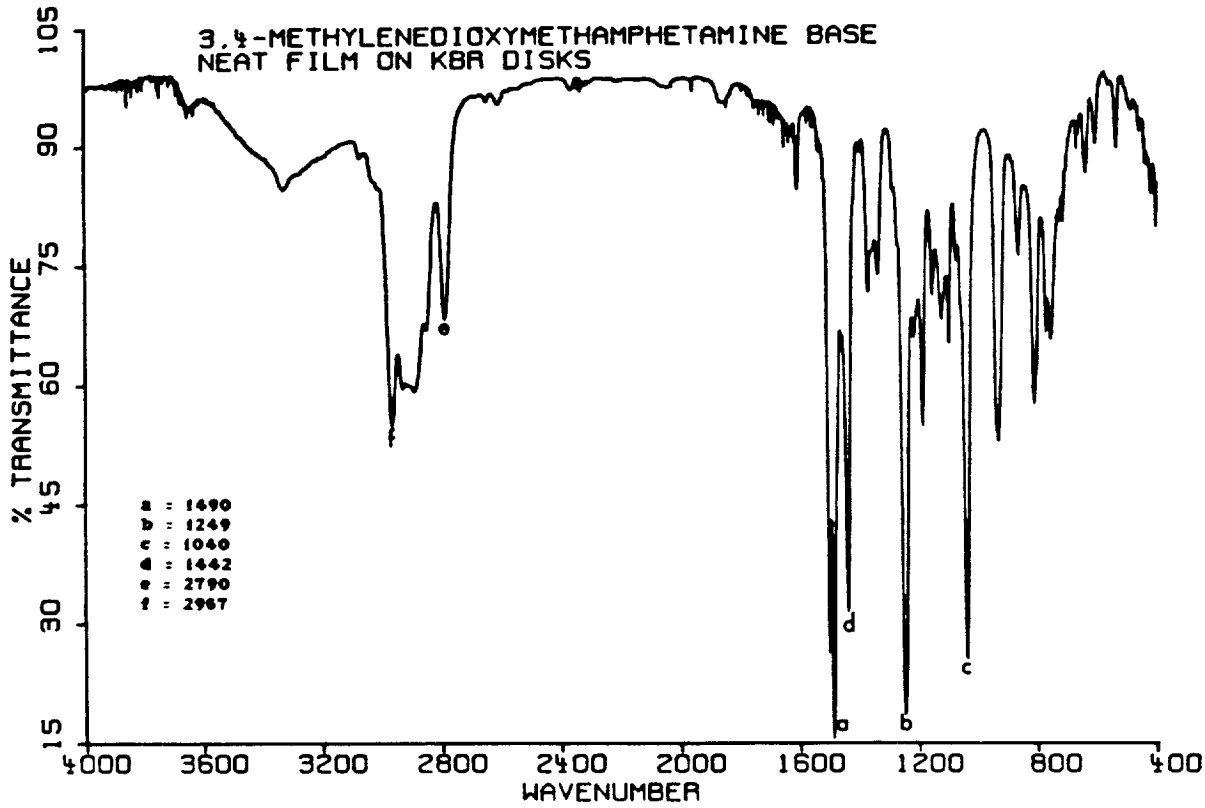
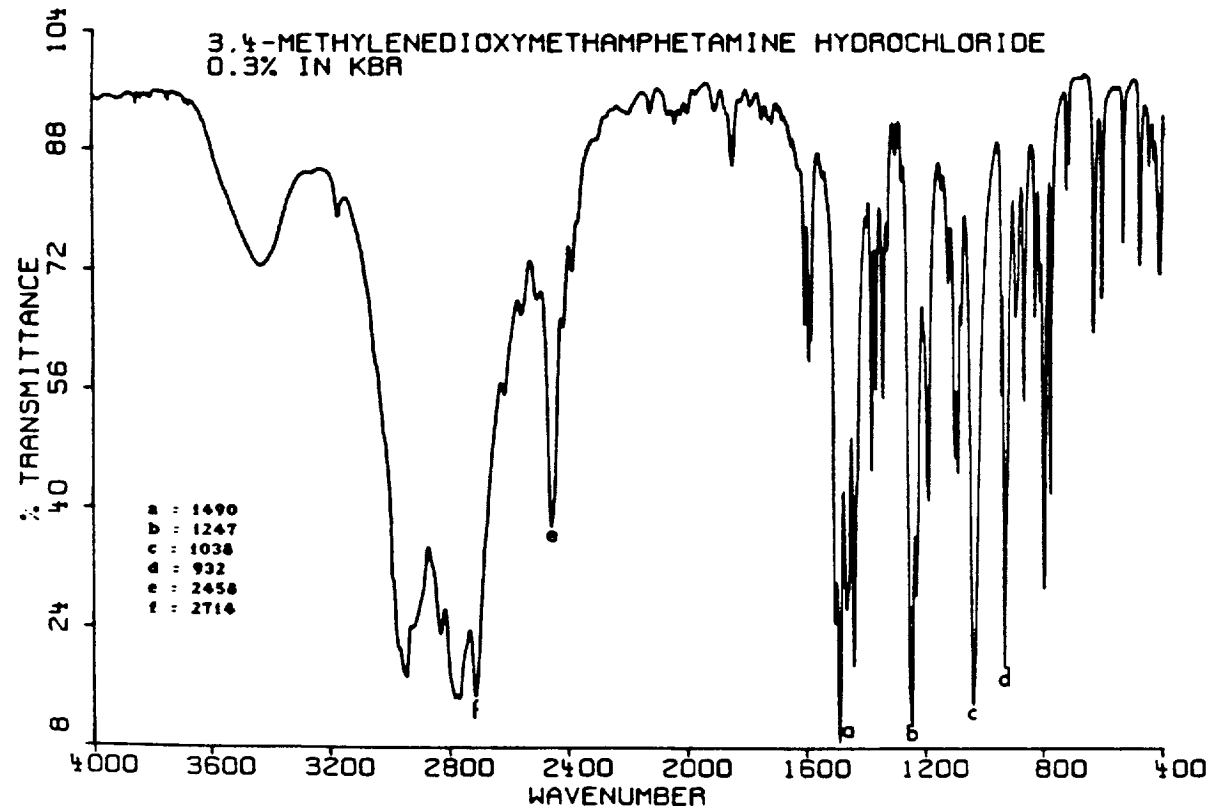
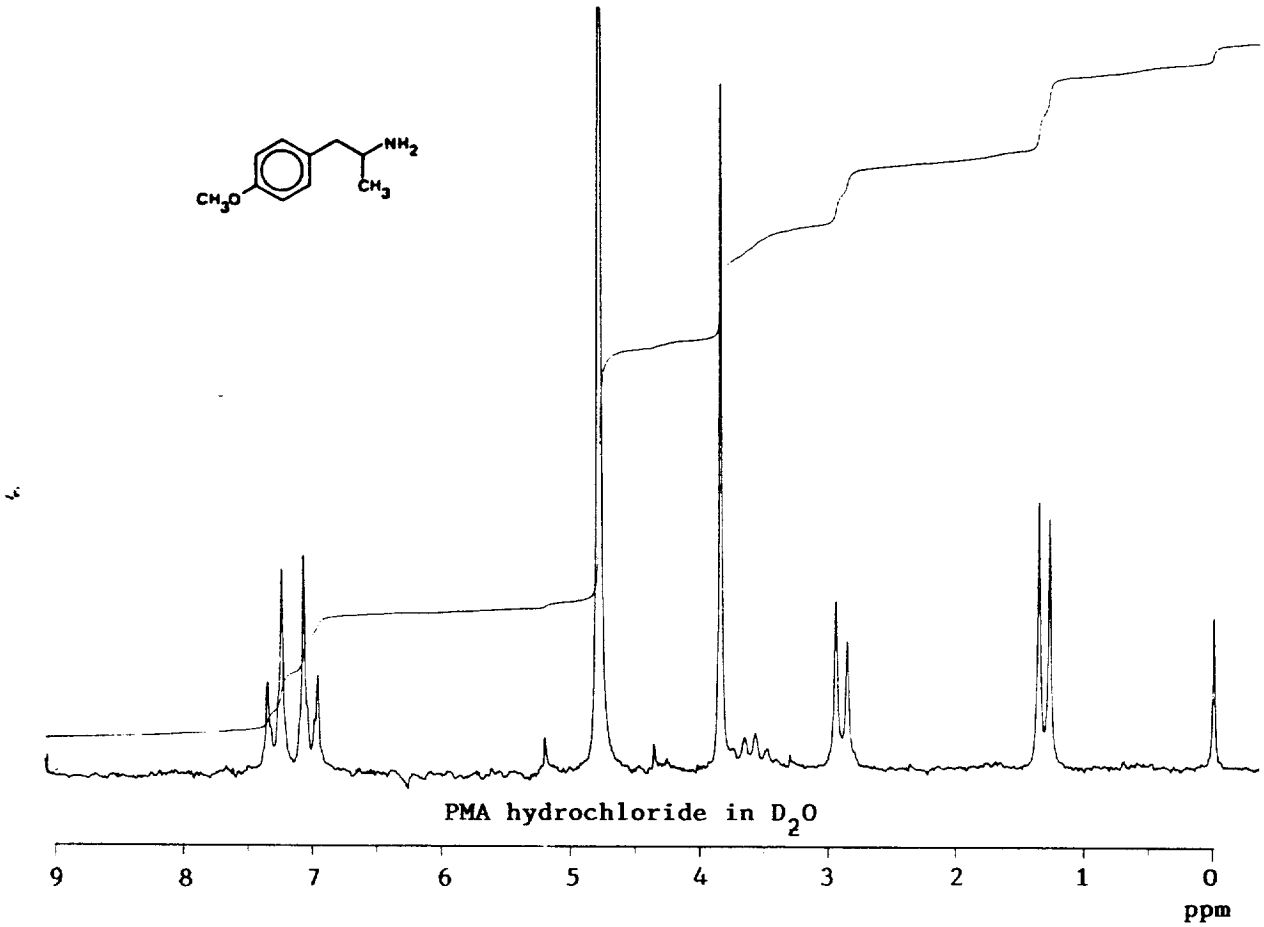
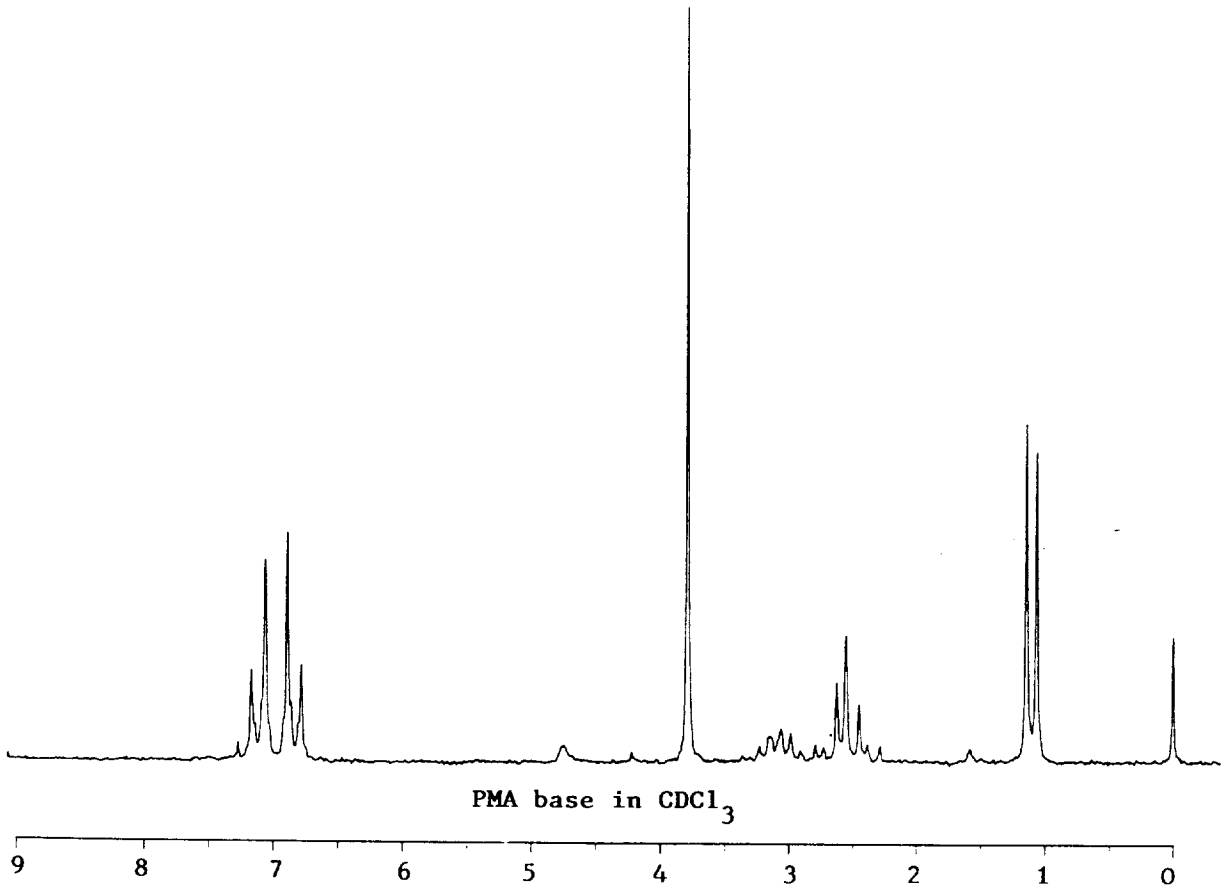
89
77
65
53
41
29
a : 1134
b : 1510
c : 1093
d : 1633
e : 1045
f : 2960
4000
3600
3200
2800
2400
2000
1600
1200
800
400
WAVENUMBER

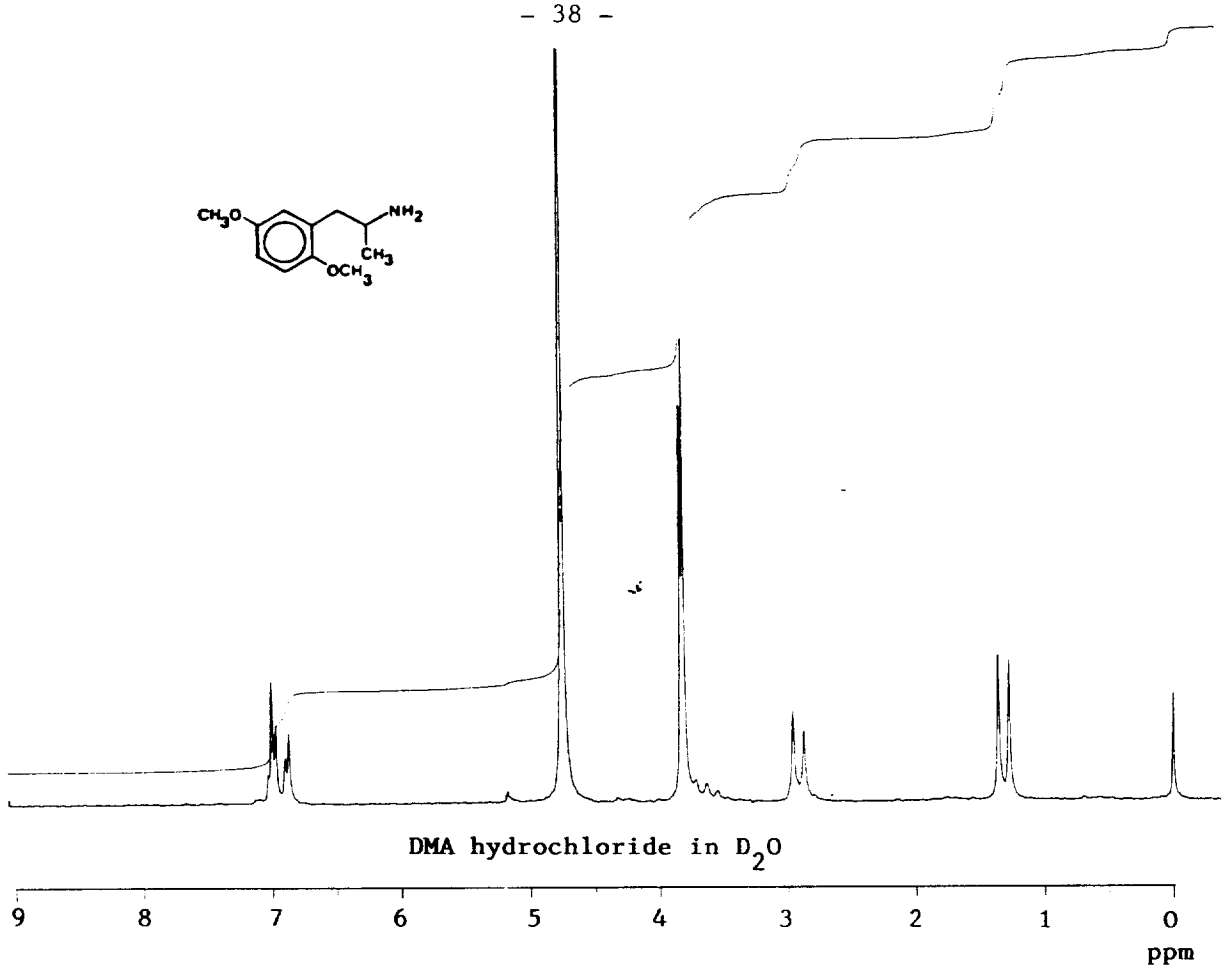

3-METHOXY-4,5-METHYLENEDIOXYAMPHETAMINE HYDROCHLORIDE
0.3% IN KBR
% TRANSMITTANCE
102
88
74
60
46
32
18
a : 1135
b : 1512
c : 1097
d : 1635
e : 1041
f : 2976
4000
3600
3200
2800
2400
2000
1600
1200
800
400
WAVENUMBER

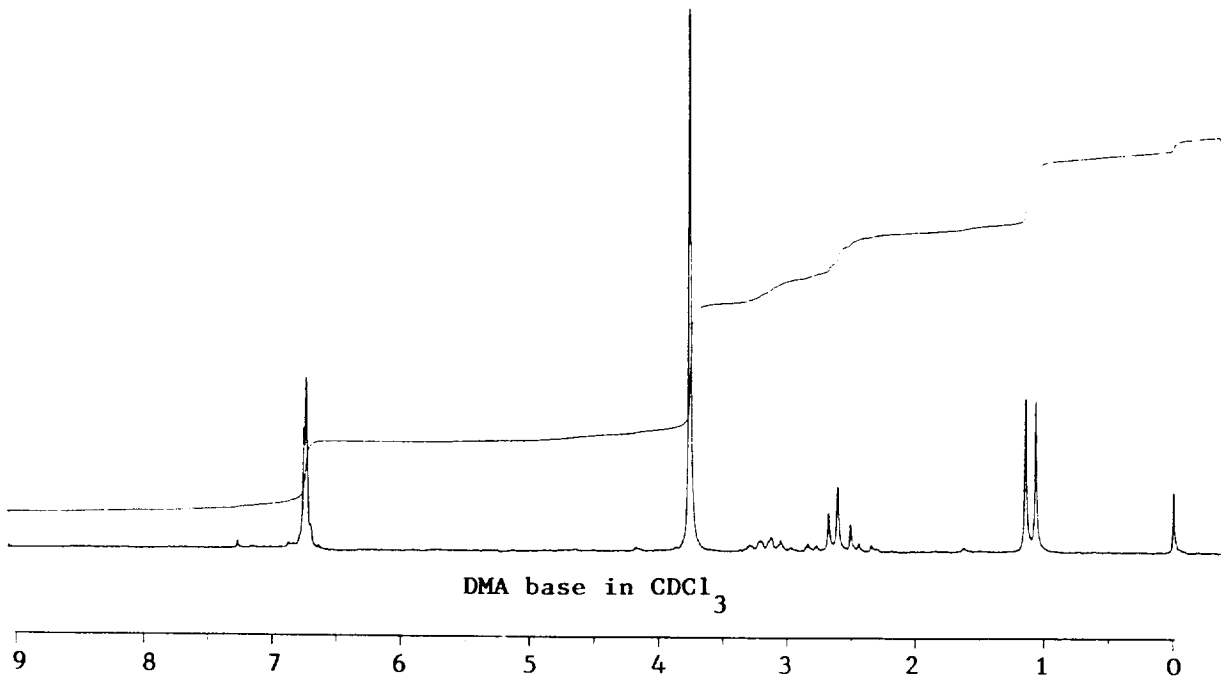

3,4-METHYLENEDIOXYMETHAMPHETAMINE BASE
NEAT FILM ON KBR DISKS
% TRANSMITTANCE
105
90
75
60
45
30
15
a = 1490
b = 1249
c = 1040
d = 1442
e = 2790
f = 2967
4000
3600
3200
2800
2400
2000
1600
1200
800
400
WAVENUMBER

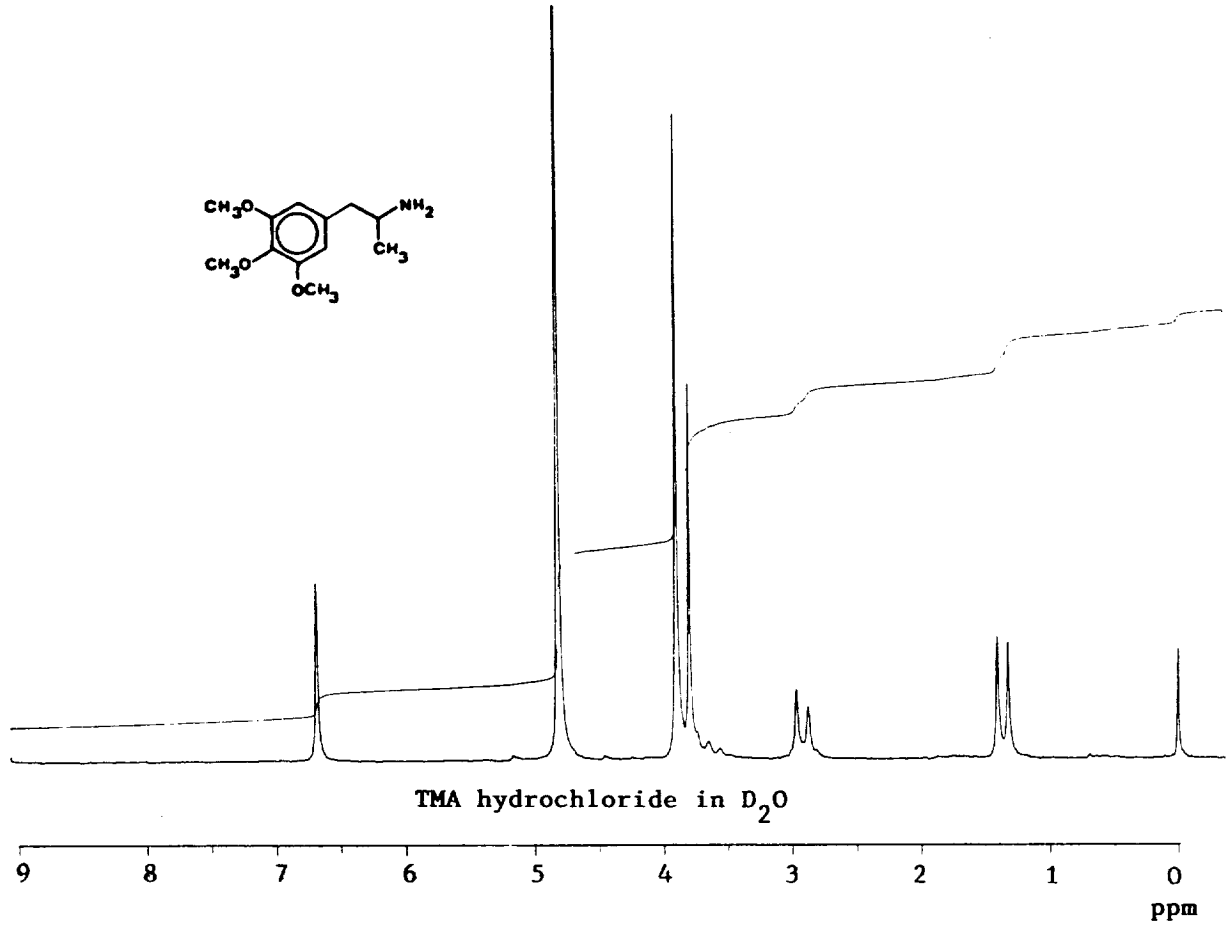

3,4-METHYLENEDIOXYMETHAMPHETAMINE HYDROCHLORIDE
0.3% IN KBR
% TRANSMITTANCE
104
88
72
56
40
24
8
a = 1490
b = 1247
c = 1038
d = 932
e = 2458
f = 2714
4000
3600
3200
2800
2400
2000
1600
1200
800
400
WAVENUMBER

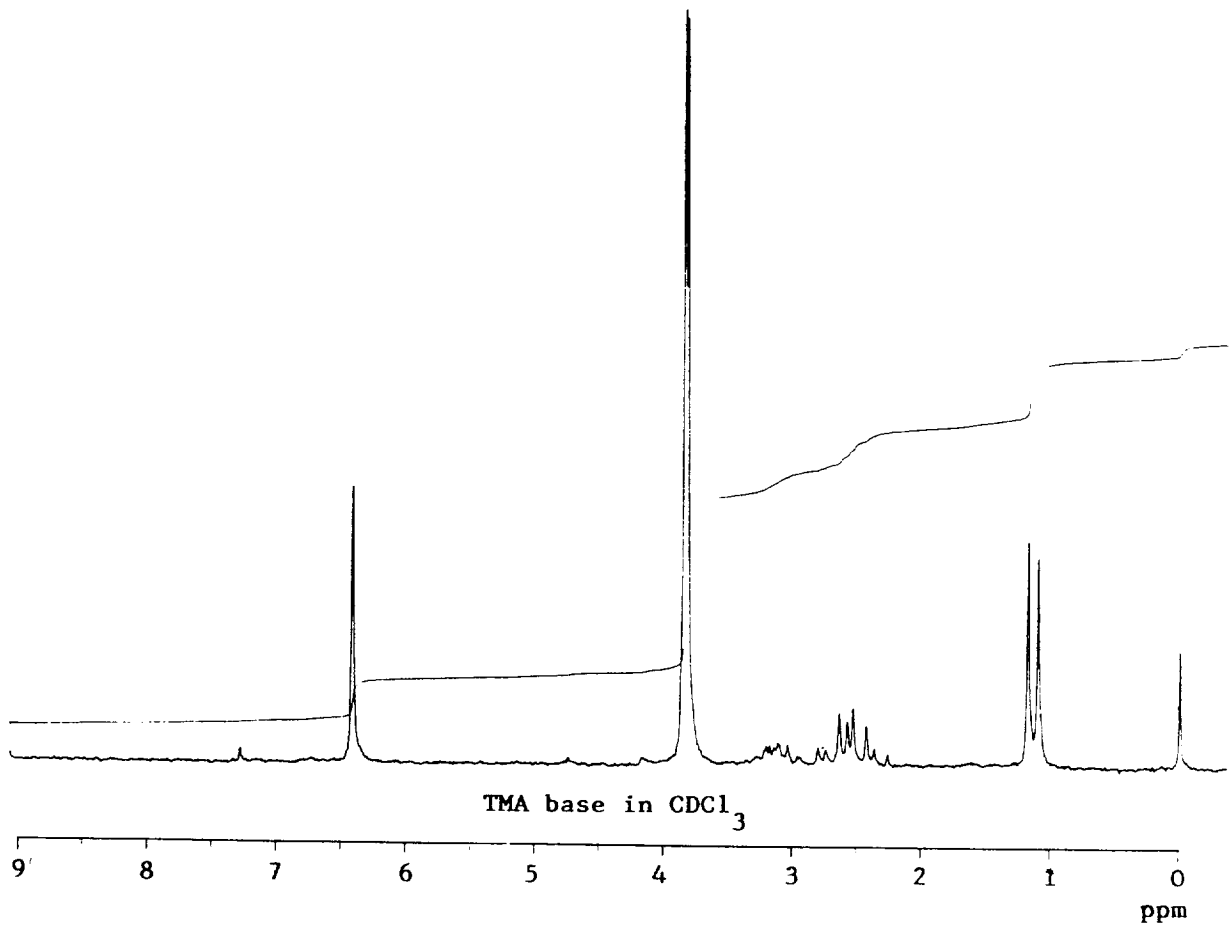

NH2
CH3
CH3O
PMA hydrochloride in D2O
9
8
7
6
5
4
3
2
1
0
ppm

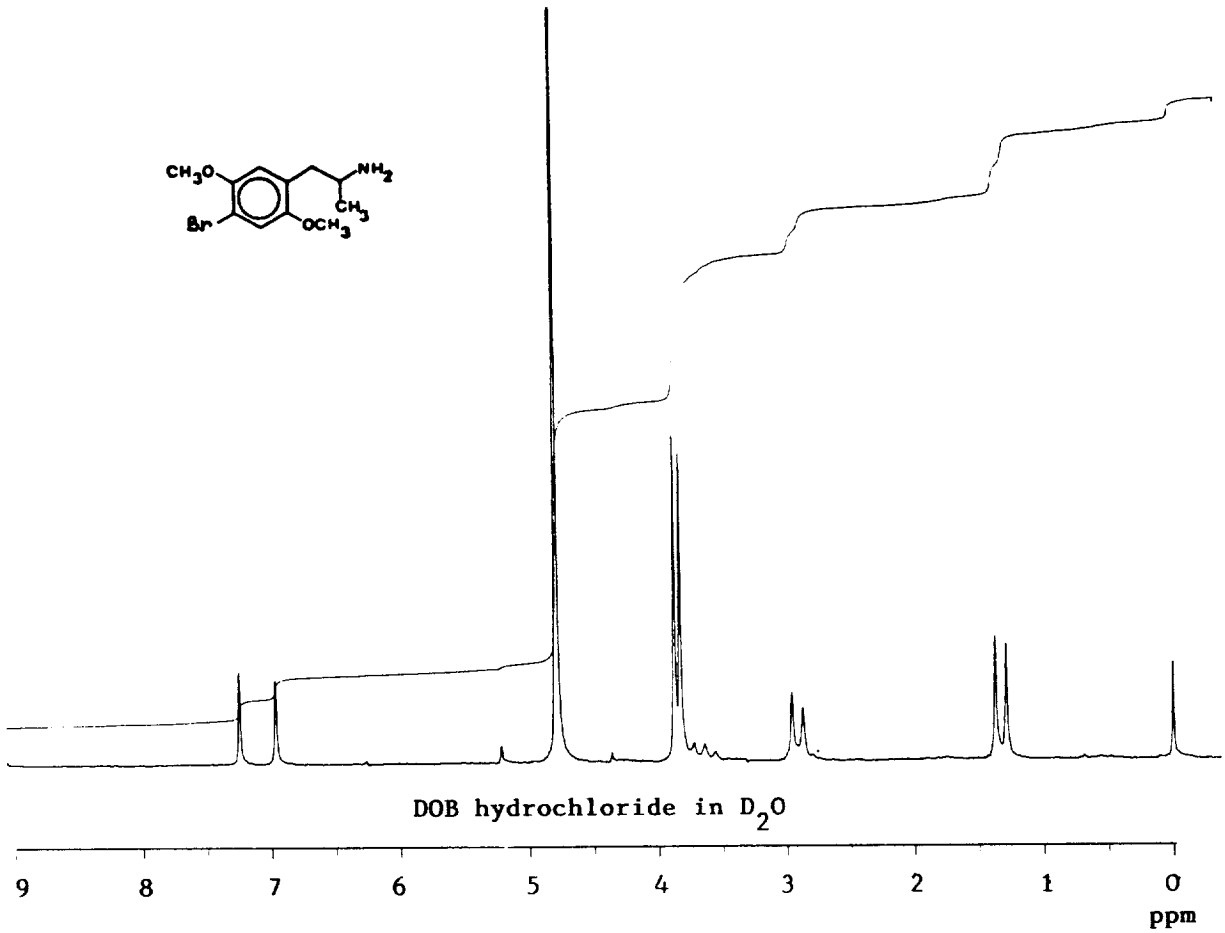

PMA base in CDCl3
9
8
7
6
5
4
3
2
1
0

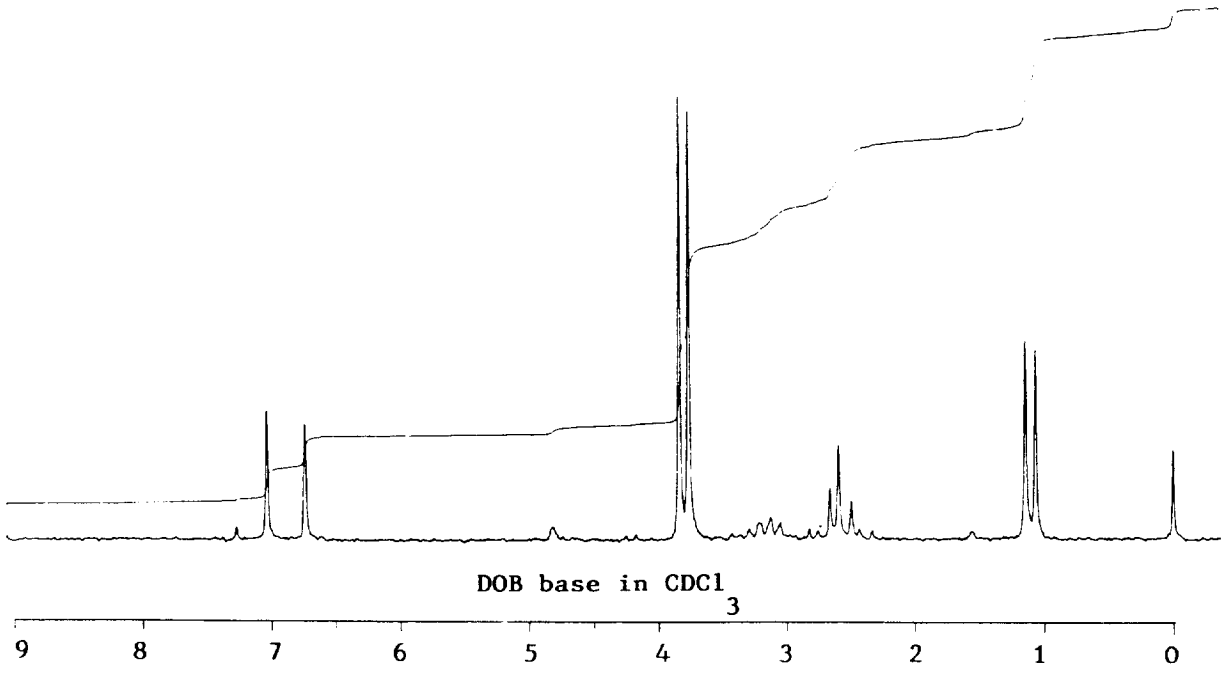

CH3O
NH2
CH3
OCH3
DMA hydrochloride in D2O
9
8
7
6
5
4
3
2
1
0
ppm

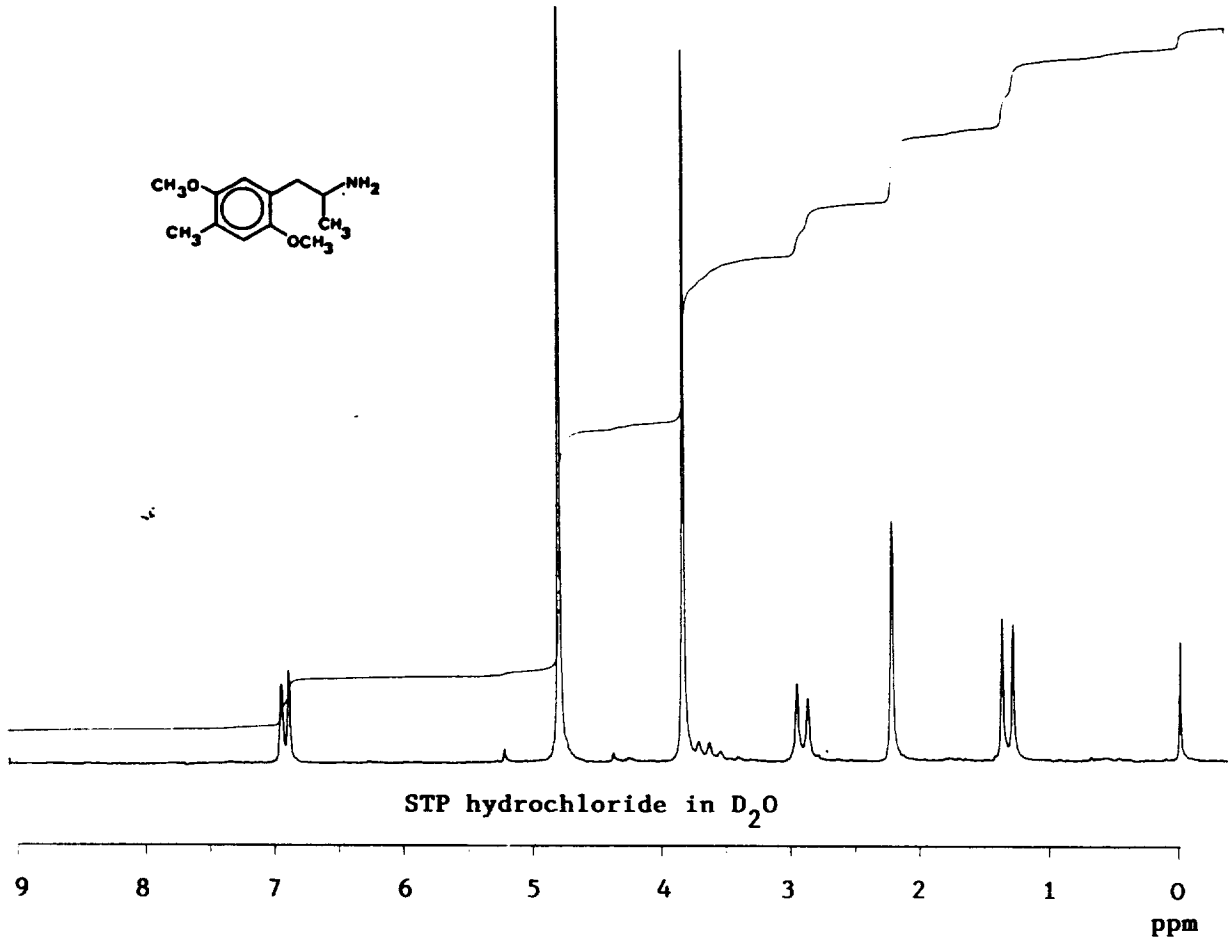

DMA base in CDCl3
9
8
7
6
5
4
3
2
1
0

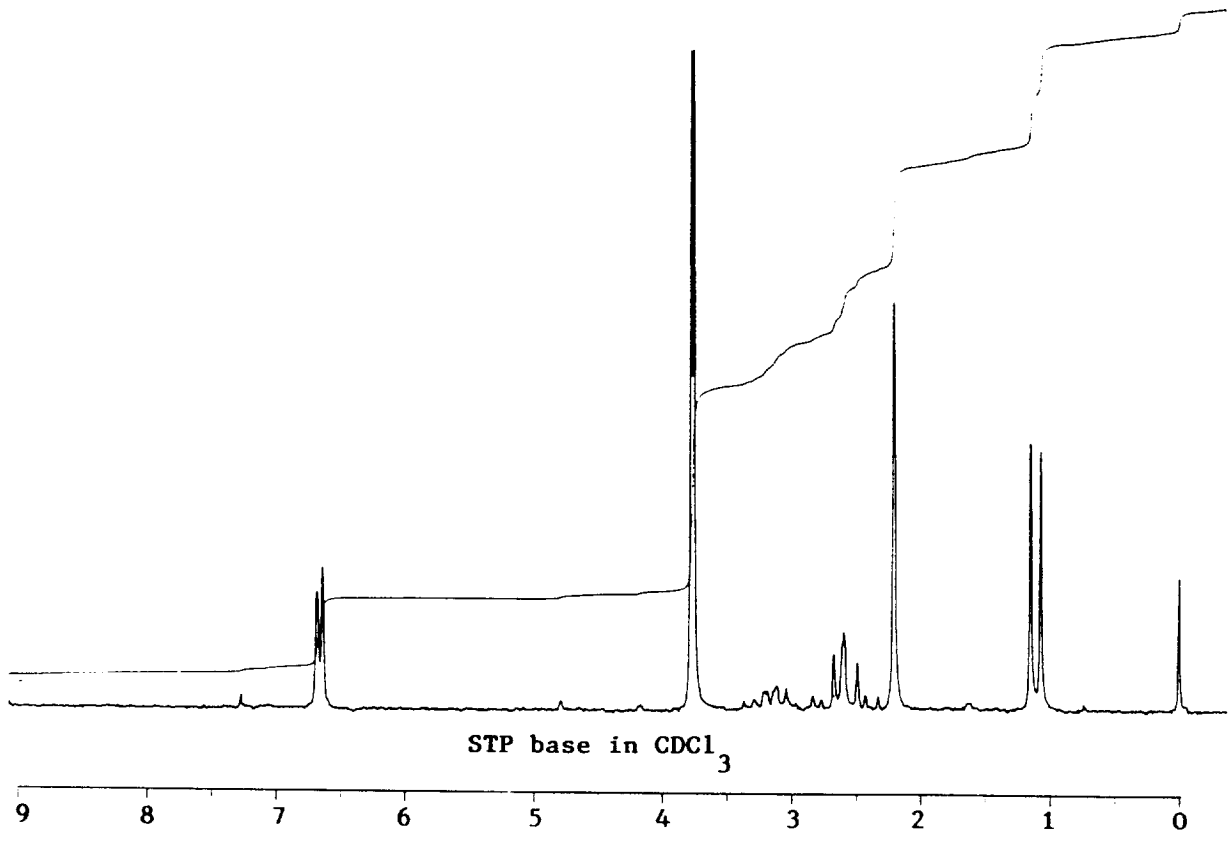

TMA hydrochloride in D_2O
9
8
7
6
5
4
3
2
1
0
ppm

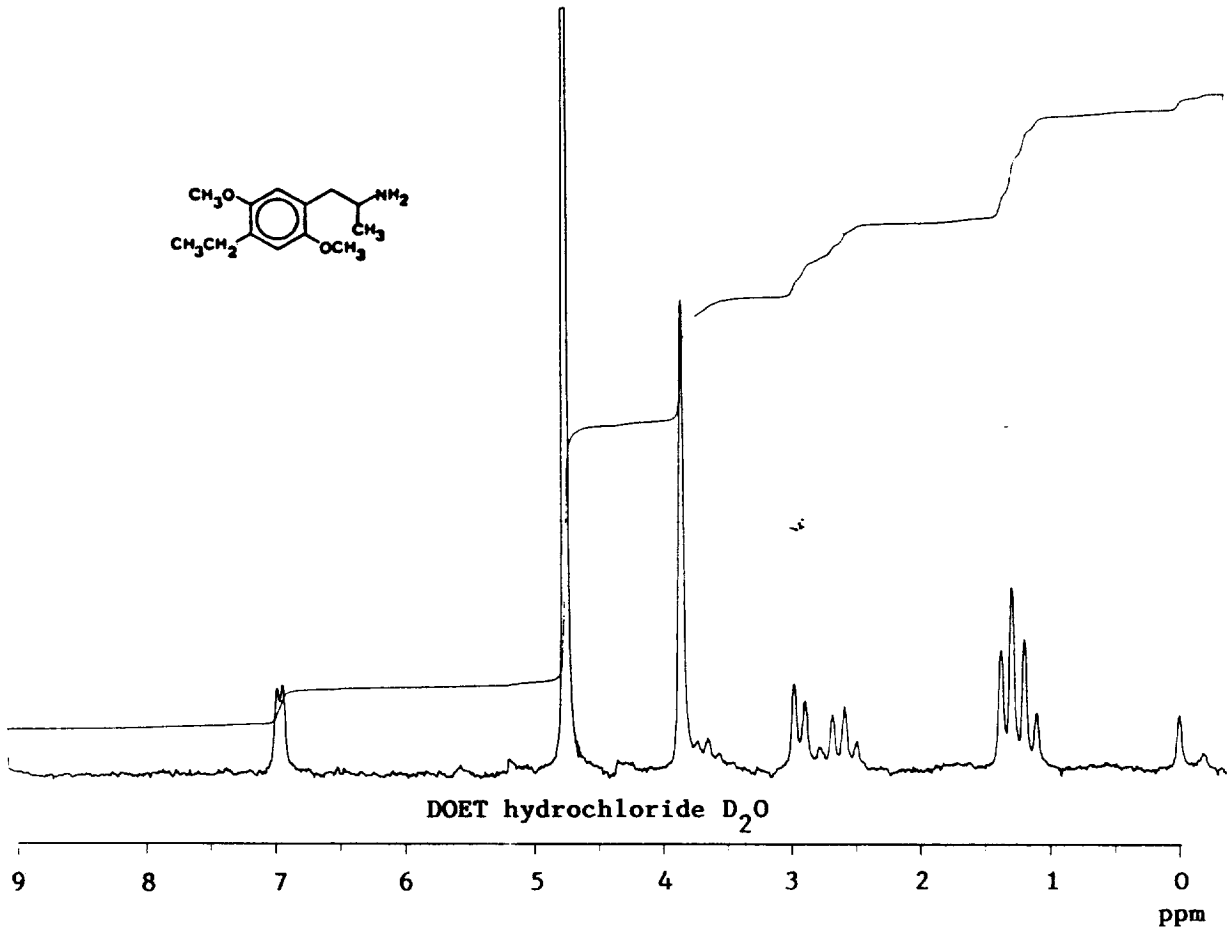

TMA base in $CDCl_3$
9
8
7
6
5
4
3
2
1
0
ppm

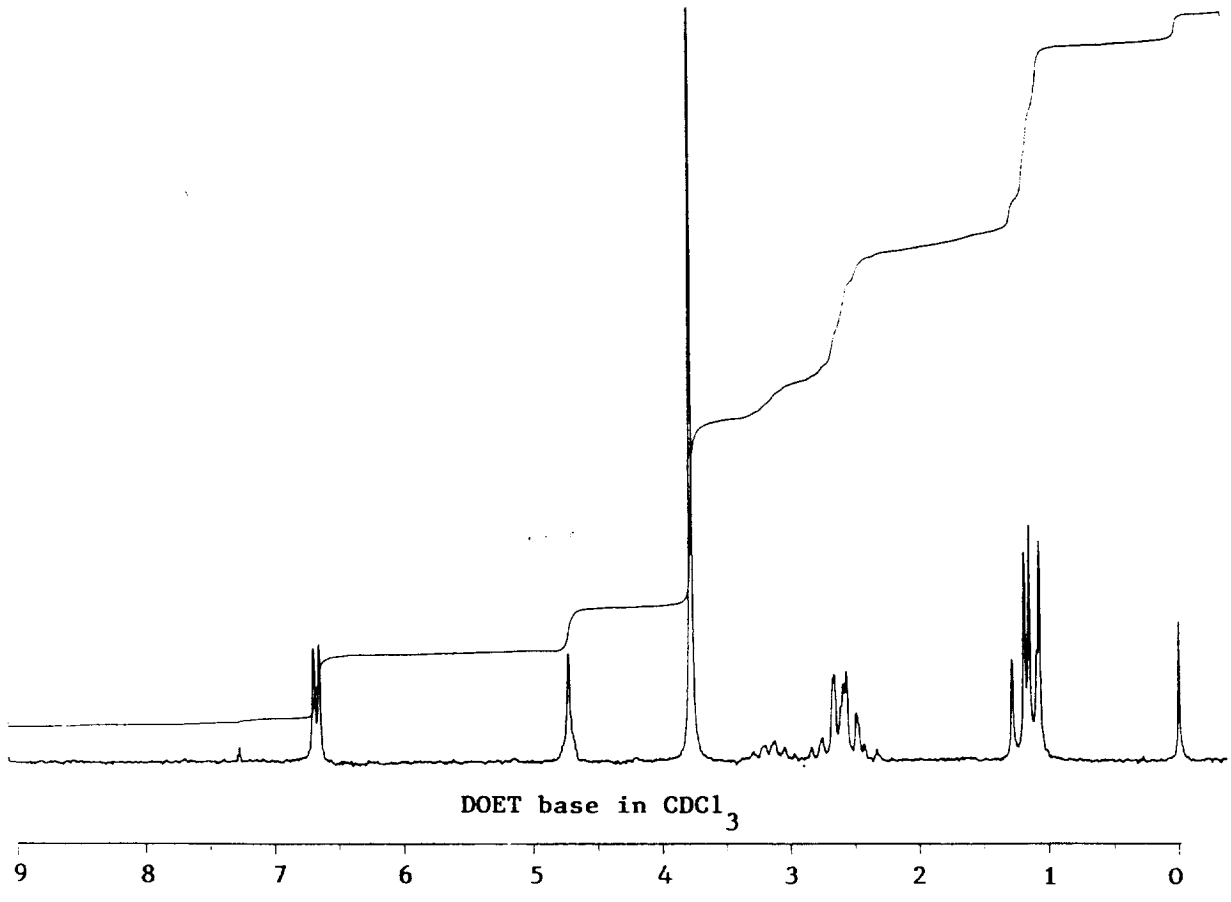

DOB hydrochloride in D_2O
9
8
7
6
5
4
3
2
1
0
ppm

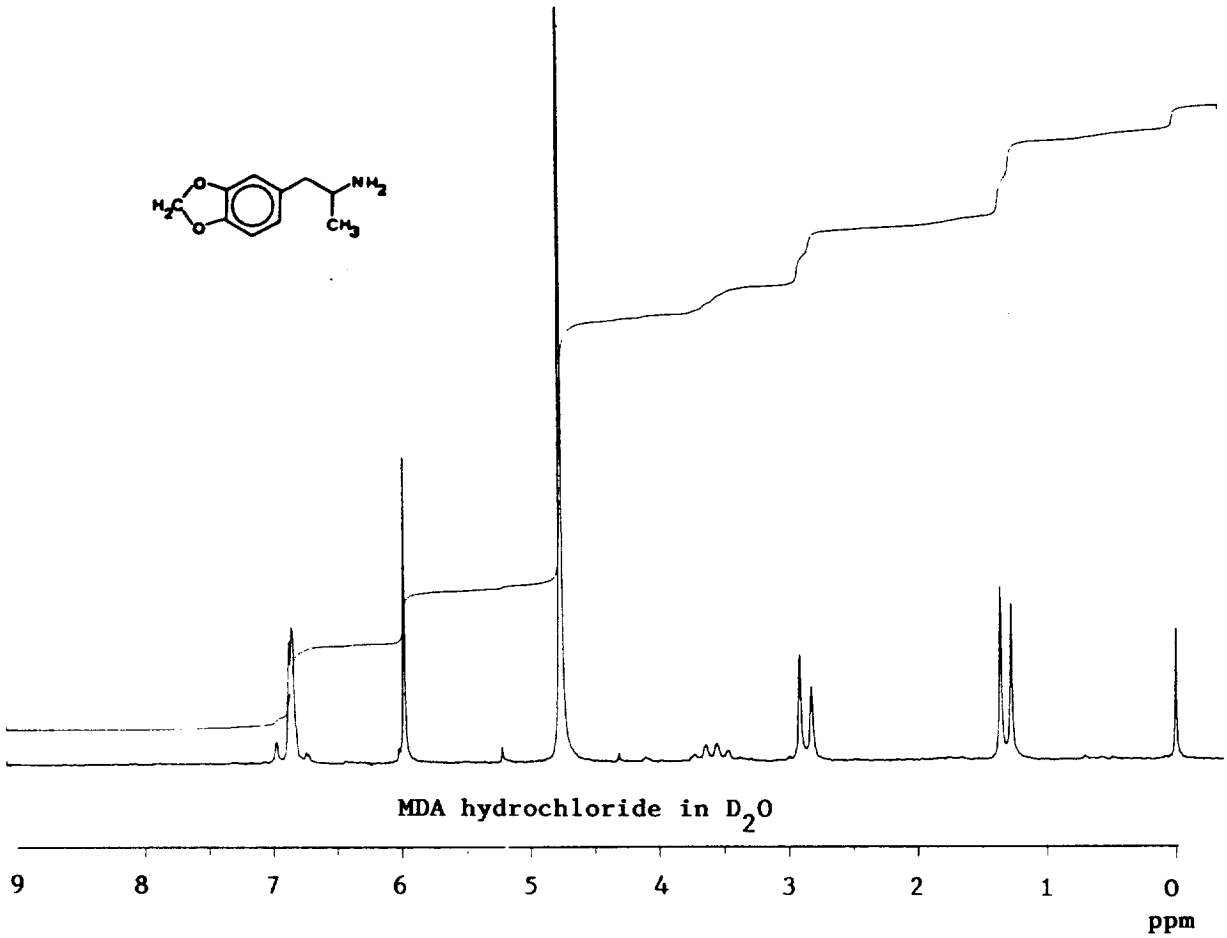

DOB base in $CDCl_3$
9
8
7
6
5
4
3
2
1
0

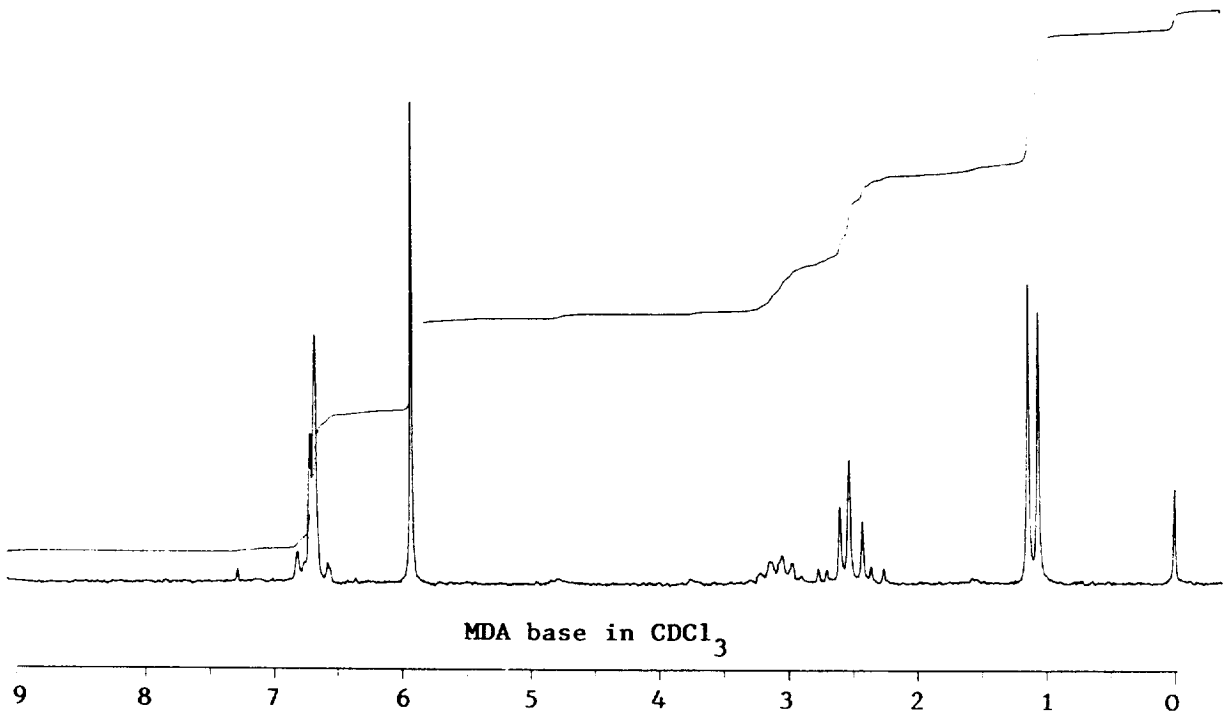

STP hydrochloride in D_2O
9
8
7
6
5
4
3
2
1
0
ppm

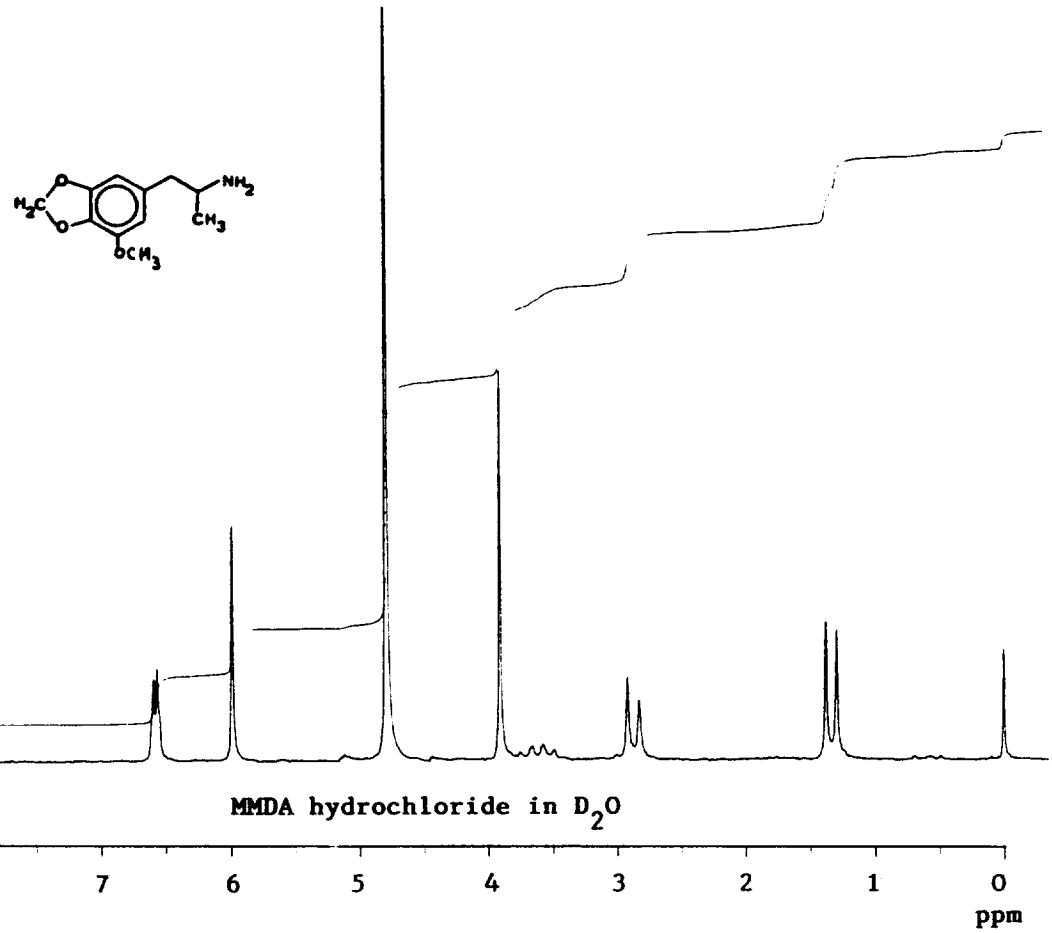

STP base in $CDCl_3$
9
8
7
6
5
4
3
2
1
0

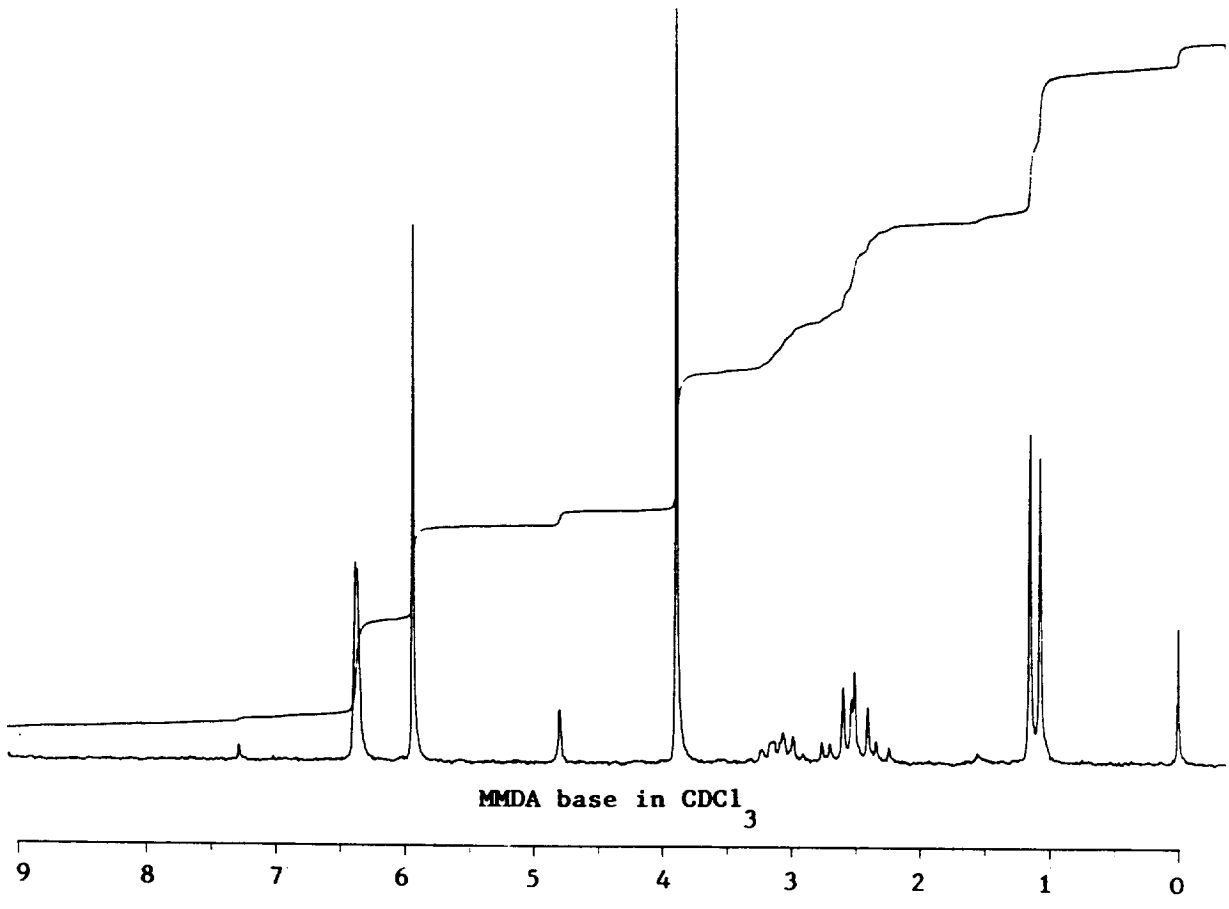

DOET hydrochloride D_2O
9
8
7
6
5
4
3
2
1
0
ppm

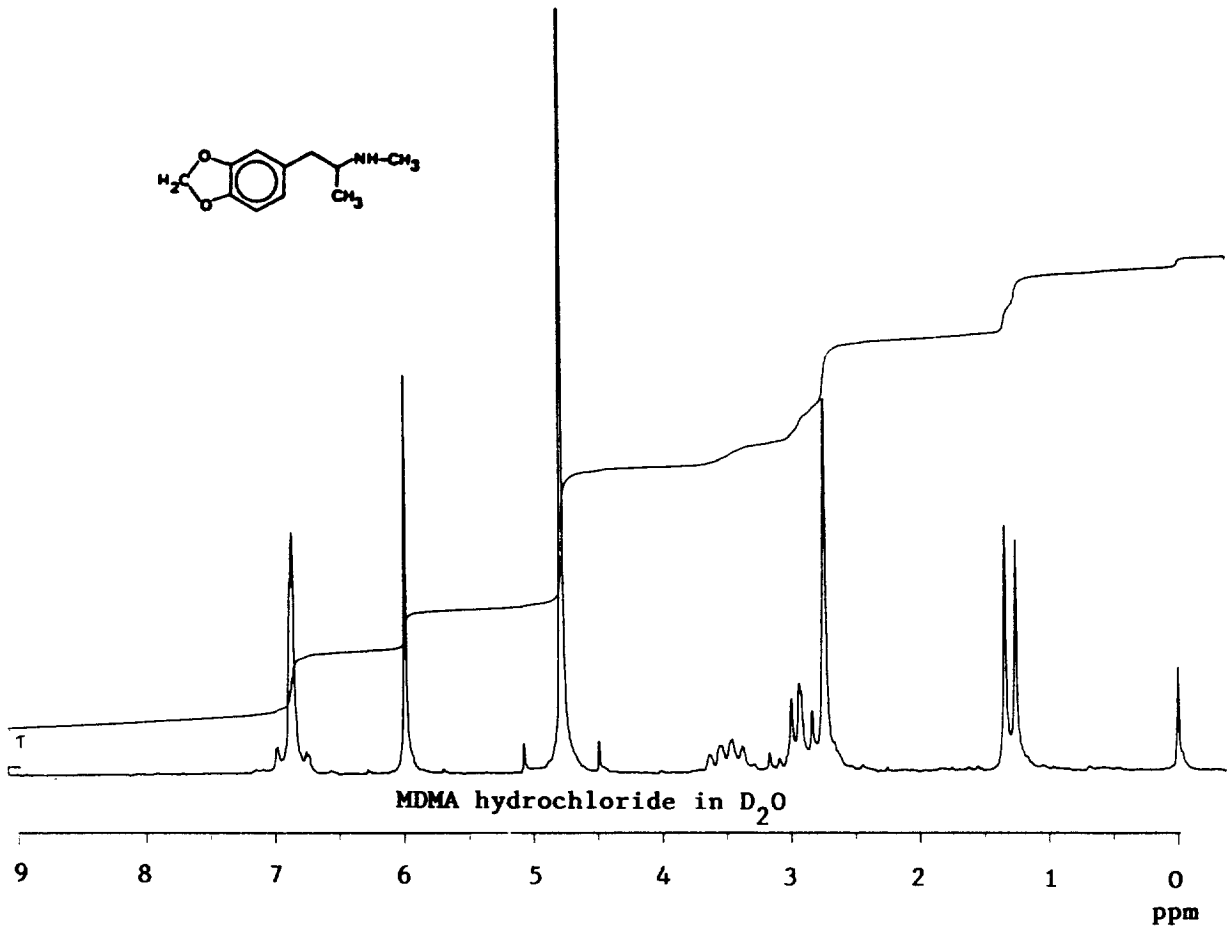

DOET base in $CDCl_3$
9
8
7
6
5
4
3
2
1
0

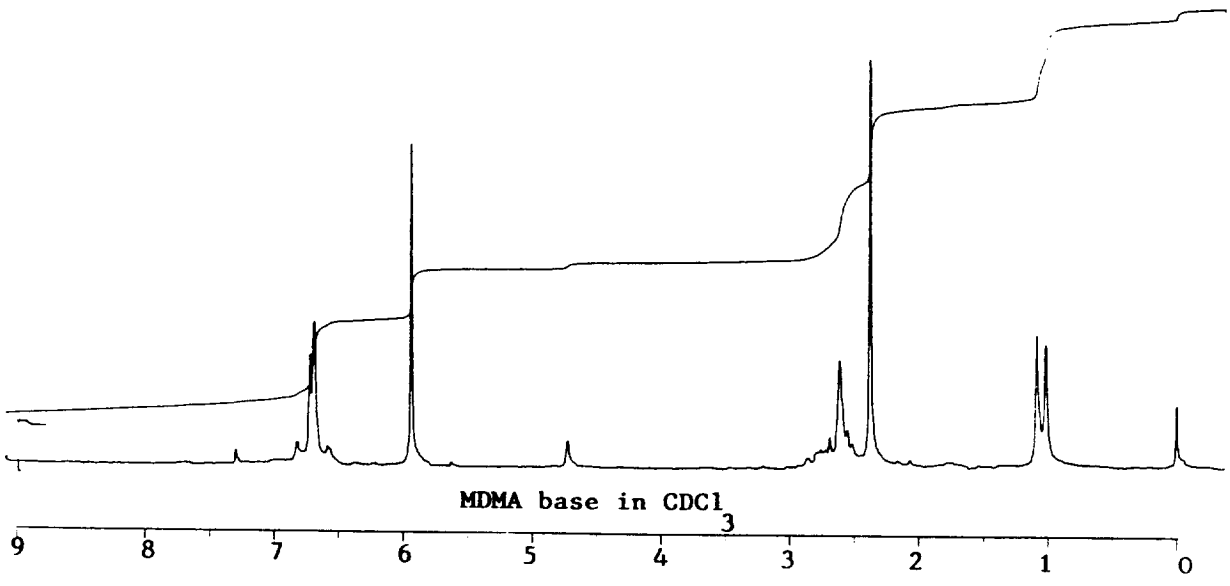

MDA hydrochloride in D_2O
9
8
7
6
5
4
3
2
1
0
ppm


MDA base in $CDCl_3$
9
8
7
6
5
4
3
2
1
0


MMDA hydrochloride in D_2O
9
8
7
6
5
4
3
2
1
0
ppm


MMDA base in $CDCl_3$
9
8
7
6
5
4
3
2
1
0


NH-CH3
CH3
MDMA hydrochloride in D2O
9
8
7
6
5
4
3
2
1
0
ppm


MDMA base in CDCl3
9
8
7
6
5
4
3
2
1
0

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