THE IDENTIFICATION OF CATHINONE AND METHCATHINONE

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The seizure of several clandestine methcathinone (ephedrone, N-methylcathinone, α-methylaminopropiophenone, "CAT") laboratories in the Upper Peninsula (U.P.) of Michigan and the continued availability of the compound in that area may be preliminary indicators of future epidemic abuse. Most recently a clandestine methcathinone laboratory was seized in the Seattle, Washington area. The former Soviet Union [1,2] has also experienced an abuse problem with "CAT". In an effort to prevent wide spread manufacture and use of "CAT" in the United States, the compound was recently placed as a temporary Schedule I drug under the Federal Controlled Substances Act [3].

Although no clandestine laboratories manufacturing cathinone (α-aminopropiophenone) have been seized by federal authorities, at least one state (Florida) lists cathinone as a controlled substance within its jurisdiction.

In order to rapidly reach a large segment of the interested forensic community, this analytical data is being presented for identification purposes with little comment. Only the synthesis routes known to have been used in clandestine laboratories are covered. Additional information and analytical data are available from Reference [1].

Synthesis and Purification

Although Zhingel [1] reported that the permanganate oxidation [Fig. 1] is used by "Russian" clandestine laboratory chemists for the conversion of ephedrine to methcathinone, all of the clandestine laboratories seized to date within this country have used the dichromate oxidation [4]. With either synthetic variation, optically active precursors should lead to optically active products: (-)1R,2S-ephedrine or (+)1S,2S-pseudoephedrine yields (-)1S-Methcathinone and (-)1R,2S-norephedrine and (+)1S,2S-norpseudoephedrine yields (-)1S-cathinone.

The amino ketones produced in this laboratory by dichromate oxidation have retained their optical activity [4]. However, Glennon et al. [5] experienced racemization using the same general technique [6]. Berrang et al. [7] report racemization of optically active cathinone during processing and Zhingel et al. [1] report that racemization can occur during synthesis or processing depending on the reaction conditions. The parameters effecting the racemization, both during synthesis and/or processing, are currently being investigated as well as the optical activity of the exhibits now being encountered in the U.P.

In any case, cathinone/methcathinone samples require care during processing since dimerization of these compounds occurs quite

readily under certain conditions [7,8,9]. These amino-ketones are stable if kept protected as the salt of a strong acid such as hydrochloric acid. However, both racemization and dimerization will occur [7] in hydroxylic solvents such as methanol, and as the free base.

The samples examined in this laboratory have been submitted as white powders, as residues or traces of material, and as liquid reaction mixtures having a dark brown to black appearance. Because the α-aminopropiophenones are sensitive to strong base, extraction of cathinone or methcathinone from aqueous mixtures using saturated sodium carbonate (pH 11) to basify the solution is preferred. Saturated sodium bicarbonate (pH 8.5) is less harsh but the evolution of larger volumes of gas, and commensurate foaming of the solution, are drawbacks to its use.

Chloroform and dichloromethane are suitable extraction solvents although clandestine laboratory operators generally use toluene. Shaking the basified aqueous solution with one of the above solvents in a separatory funnel will effect transfer of the cathinone or methcathinone as the free base into the organic solvent. The solvent should then be passed through a layer of anhydrous sodium sulfate to remove any basic aqueous phase remaining in the extraction solvent. Addition of an isopropyl or ethyl alcohol: hydrochloric acid mixture (4:1) to the extracted base, and subsequent solvent evaporation with a steam bath, is suitable to provide the hydrochloride salt. If available, a rotary vacuum evaporator is useful at this stage. Recrystallization may be accomplished, if necessary, from isopropyl alcohol to which diethyl ether or THF is added.

Instrumentation

Acquisition of the ultraviolet (UV) spectra in ethanol was accomplished with a Perkin-Elmer Lambda 6 Spectrophotometer. Infrared (IR) spectra were obtained using a Perkin-Elmer 1800 Fourier Transform Infrared Spectrophotometer. Melting points were recorded on material dried over silica gel under vacuum using a Thomas-Hoover "unimelt" apparatus. Gas Liquid Chromatographic retention times were acquired using a Hewlett-Packard 5890 with FID. The Mass Spectra were obtained from a Hewlett-Packard 5970 Mass Selective Detector having a 10 m x 0.25 mm x 1 μm DB-1 column.

Color Tests

The color tests were performed on approximately 5 mg of the pure hydrochloride salts in a porcelain spot plate. (Table 1).

Ultraviolet Spectrophotometry (UV)

Cathinone HCl or methcathinone HCl (Fig. 2A) in ethanol display a UV spectrum markedly different than the typical UV spectra for the amphetamine HCl, methamphetamine HCl, norephedrine HCl, and ephedrine HCl (Fig. 2B) series of compounds. Cathinone and methcathinone have extended conjugation due to the carbonyl group adjacent to the phenyl ring and show maxima at 245 and 203 nm and a minima at 217 nm.

Infrared Spectroscopy (IR)

The IR Spectra of cathinone HCl and methcathinone HCl are provided in Fig. 3A and 3B respectively using the standard potassium bromide matrix. An intense carbonyl absorption can be seen in both compounds at 1688 cm^{-1}. The weak absorption at about 3360 cm^{-1} is probably due to a small amount of the enol tautomer being present, rather than contamination from unreacted aminoalcohol precursors.

Melting Points

Optically active cathinone HCl melted at 179-180 °C turning red and effervescing. Optically active methcathinone melted at 176-178 °C turning brown and effervescing.

GLC

Although either HP-1 or HP-17 columns are suitable for quantitation using propiophenone (phenyl-1-propanone, P-1-P) or phenyl-2-butanone (P-2-B) as internal standards, both screening and quantitations have been on the HP-1 column at this laboratory (Table 2).

GC-MS

The hydrochloride salts of cathinone, amphetamine, norephedrine, norpseudoephedrine, methcathinone, methamphetamine, ephedrine and pseudoephedrine were dissolved in water, basified with sodium carbonate, extracted with chloroform and passed through anhydrous sodium sulfate. The representative mass spectra are presented in Fig. 4A. Because the mass spectra of some of the above compounds are similar, acetylated mass spectra are shown in Fig. 4B. The formula weights for both groups of compounds are shown in Table 3.

Acetylation was accomplished by one of two procedures. The solutions, extracted as above, were placed in a beaker and evaporated to near dryness. Sufficient acetic anhydride was added to cover the material which was heated on a steam bath until the excess acetic anhydride evaporated. A simpler procedure yielding identical results was to draw a 1/2 µL plug of the extracted sample into a micro syringe followed by a 1/2 µL plug of acetic anhydride. The simultaneous injection of the two components into the hot injection port provides "on column" acetylation. Acetylated norephedrine, ephedrine and their diastereomeric pseudo isomers show multiple GLC peaks with the corresponding mass spectra indicating reaction at the hydroxyl or the amino group, or both groups. Due to the similarity of the mass spectra of norephedrine and ephedrine with their diastereomeric pseudo compounds, the latter are not included in Figure 4A and 4B. The mass spectra are provided for comparative purposes without further comments.

Discussion

Cathinone and methcathinone are potent stimulants which are structurally related to the controlled substances amphetamine and methamphetamine. All four stimulants can be synthesized from the respective precursors, norephedrine or norpseudoephedrine, and pseudoephedrine or ephedrine. Infrared spectroscopy provides an excellent means of distinguishing between these compounds.

Identification of the aminoketones by GC-MS is somewhat more difficult. The use of an acetylating technique will give the analyst more easily distinguishable mass spectra, in addition to a second retention time. Additionally the combination of the color tests previously described, especially when used in conjunction with UV spectroscopy, should leave no doubt which class of compounds is being analyzed.

As noted earlier, cathinone and methcathinone require care during purification. Extractions should proceed as rapidly as possible and the organic phase, containing the free base aminoketone, should be dried with anhydrous sodium sulfate. Although it is preferable to immediately convert the compounds into a stable salt form, the free bases in chloroform or dichloromethane kept at 0°C showed no obvious signs of decomposition after 48 hours. "Noticeable decomposition" is evident by a yellowing of the solution. Lack of stability of both the base and hydrochloride forms of the aminoketones in alcohol solutions has also been mentioned and storage in these solvents is not recommended. Breakdown, however, has not been found to be so rapid as to preclude the use of alcohols as solvents for UV spectra.

REFERENCES

[1] Zhingel, K. Y., Dovensky, W., Crossman, A., and Allen, A., "Ephedrone: 2-Methylamino-1-Phenylpropan-1-one(Jeff)," *Journal of Forensic Sciences*, Vol. 36, No. 3, May 1991, pp. 915-920.

[2] Savenko, V.G., Semkin, E.P., Sorokin, V.I., and Kazankov, S.P., "Expert Examination of Narcotic Substances Obtained from Ephedrine", The All-Union Scientific Research Institute of the U.S.S.R. Ministry of the Interior. Moscow, 1989; pp. 1-24.

[3] Federal Register, Vol. 57, May 1, 1992, 57FR188824.

[4] U.S. Patent 2,802,865, L'Italien, Yvon J., and Rebstock, Mildred C., assigned to Parke, Davis and Co., Detroit, Michigan, Aug. 13, 1957.

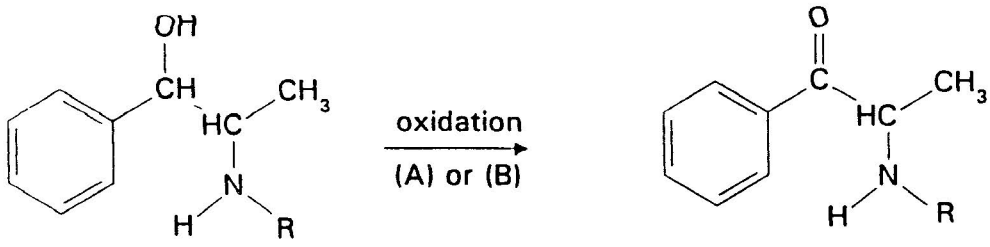
[5] Glennon, R. A., Yousif, Mamoun, Naiman, Norren, and Kalix, Peter "Methcathinone: A New and Potent Amphetamine-Like Agent," *Pharmacology Biochemistry & Behavior*, Vol.26, 1986, pp.547-551.

[6] British Patent 768.772, Feb. 20, 1957.

[7] Berrang, B.D., Lewin, A.H., and Carroll, F.I., "Enantiomeric α-Aminopropiophenones(cathinone):Preparation and Investigation," *The Journal of Organic Chemistry*, Vol. 47, 1982, pp. 2643-2647.

[8] Hartung, Walter H., Munch, James C., Deckert, W. Allen, Crossley, Frank, "Amino-Alcohols. II. Homologs and Analogs of Phenylpropanolamine", *Journal of the American Chemical Society*, Vol. 52, Aug. 1930, pp. 3317-3322.

[9] MNAR/11/75 "Studies on the Chemical Composition of Khat. III. Investigations on the phenylalkylamine Fraction." Report on research being carried out at the United Nations Narcotics Laboratory, Geneva.



R = H for norephedrine or norpseudoephedrine and Cathinone
R = CH_3 for ephedrine or pseudoephedrine and Methcathinone

A) Potassium permanganate / acetic acid
B) Sodium dichromate / sulphuric acid

Figure 1 - Synthesis of Cathinone and Methcathinone

TABLE 1: COLOR TESTS

	MARQUIS[1]	SECONDARY[2] AMINE	CHEN'S[3]
Cathinone	No reaction	No reaction	Slow forming, yellow-orange
Amphetamine	Orange to brown	No reaction	No reaction
Norephedrine	No reaction	No reaction	Purple
Methcathinone	No reaction	Slt. ppt. of blue flecks or blue ring formed	Slow forming, yellow-orange
Methamphetamine	Orange to brown	Dark blue	No reaction
Ephedrine	No reaction	No reaction	Purple

1 Marquis Reagent: 2 drops of formaldehyde solution (37%) with 1 mL of concentrated sulfuric acid.
Ref.: E.G.C. Clarke, ed., Isolation and Identification of Drugs, London, Pharmaceutical Press, 1969, p. 801.

2 Secondary Amine Reagents: Reagent 1 - 1% sodium nitroprusside in water to which 10% by volume of acetaldehyde is added;
Reagent 2 - 2% solution of sodium carbonate.
Ref.: Fiegel, F., Spot Tests in Organic Analysis, Elsevier Publishing Co., New York, 1966, p. 251.

Directions: Add 1-2 drops of Reagent 1 to the sample followed by 1-2 drops of Reagent 2.

3 Chen's Reagents: Reagent 1 - 1% acetic acid in water;
Reagent 2 - 1% copper sulfate in water;
Reagent 3 - 2N sodium hydroxide solution
Ref.: (See Ref. 2 above) p. 131.

Directions: Add 1-2 drops of Reagent 1 to the sample, followed by 1-2 drops of Reagent 2, followed by 1- 2 drops of Reagent 3.

TABLE 2: GLC DATA

	HP-1[1] RT IN MIN	HP-17[2] RT IN MIN
Amphetamine	1.51	1.15
P-1-P	1.84	1.52
Methamphetamine	2.19	1.33
P-2-B	2.64	1.98
Cathinone	4.57	3.55
Methcathinone	5.55	3.54
Norephedrine	5.93	3.90 (Tailing)
Ephedrine	7.18	4.24 (Tailing)

1) HP-1 5 m X 0.53 mm X 2.65 μm, 80°C initial temp. 8.5 min., rate 25°C/min to 250°C, 1 min hold. FID detector at 265°C. Injector temperature at 250°C. Split mode.

2) HP-17 10 m X 0.53 mm X 2.0 μm, 140°C initial temp. 6.0 min., rate 30°C/min. to 250°C, 1 min hold. FID detector at 265°C. Injector temperature at 250°C. Split mode.

TABLE 3

Formula Weights (F.W.) for methcathinone and related compounds.

COMPOUND	F.W.
1. Cathinone	149
1a. N-acetylcathinone	191
2. Amphetamine	135
2a. N-acetylamphetamine	177
3. Norephedrine	151
3a. N-acetylnorephedrine	193
3b. O-acetylnorephedrine	193
3c. N,O-diacetylnorephedrine	235
4. Methcathinone	163
4a. N-acetylmethcathinone	205
5. Methamphetamine	149
5a. N-acetylmethamphetamine	191
6. Ephedrine	165
6a. N-acetylephedrine	207
6b. O-acetylephedrine	207
6c. N,O-diacetylephedrine	249

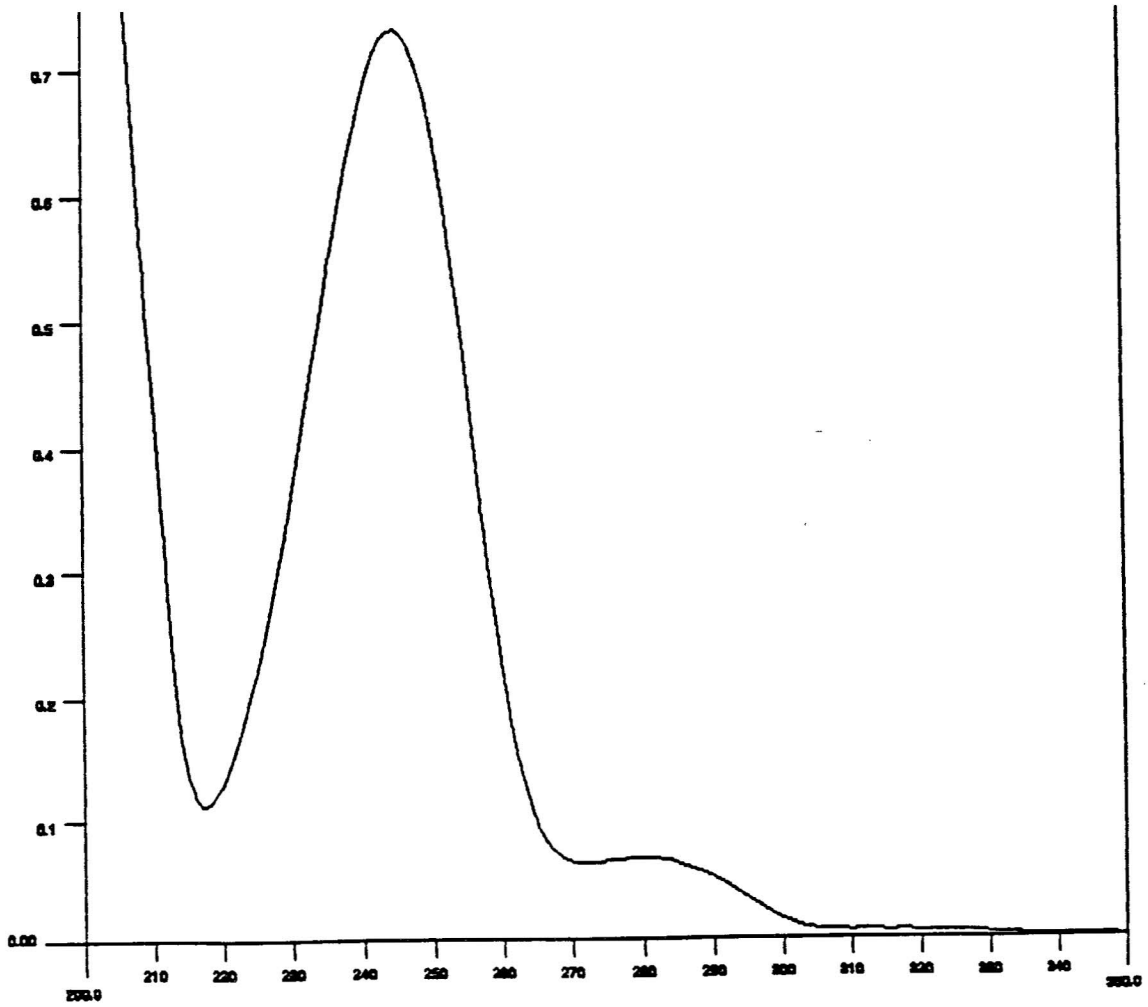


FIGURE 2A - UV SPECTRA (CATHINONE/METHCATHINONE TYPE)

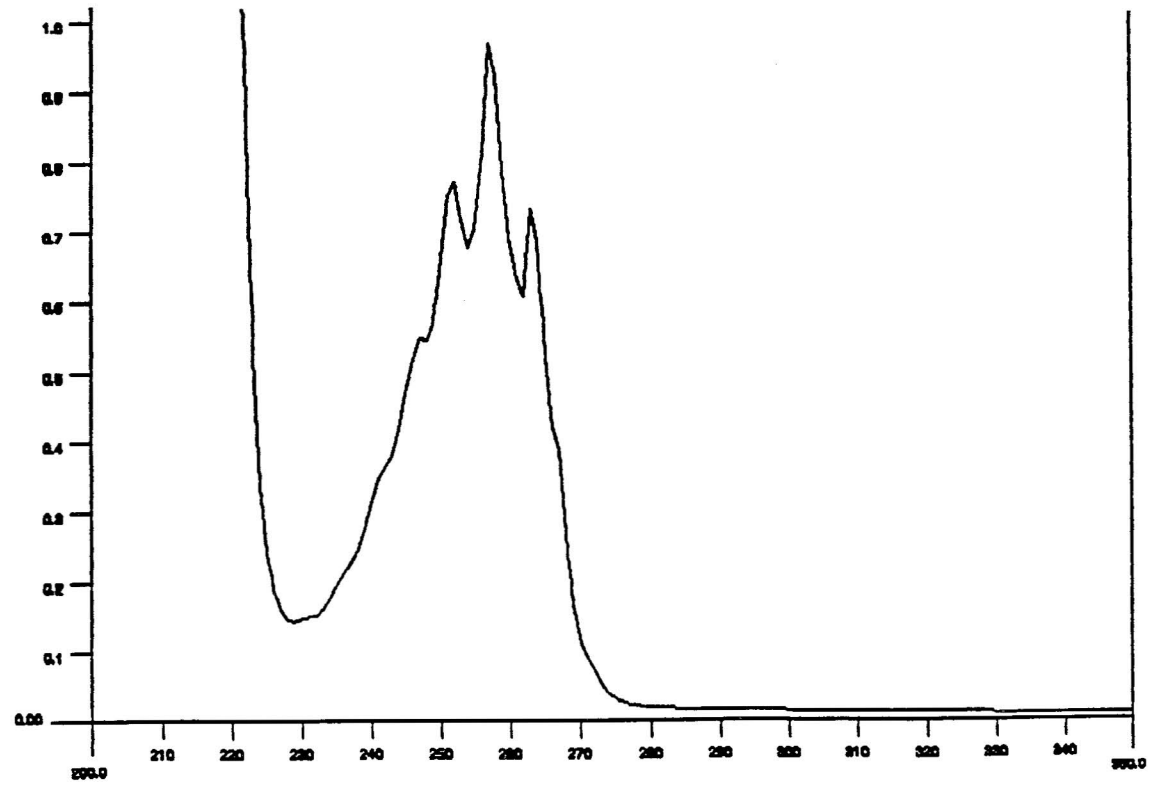


FIGURE 2B - UV SPECTRA (EPHEDRINE/METHAMPHETAMINE TYPE)

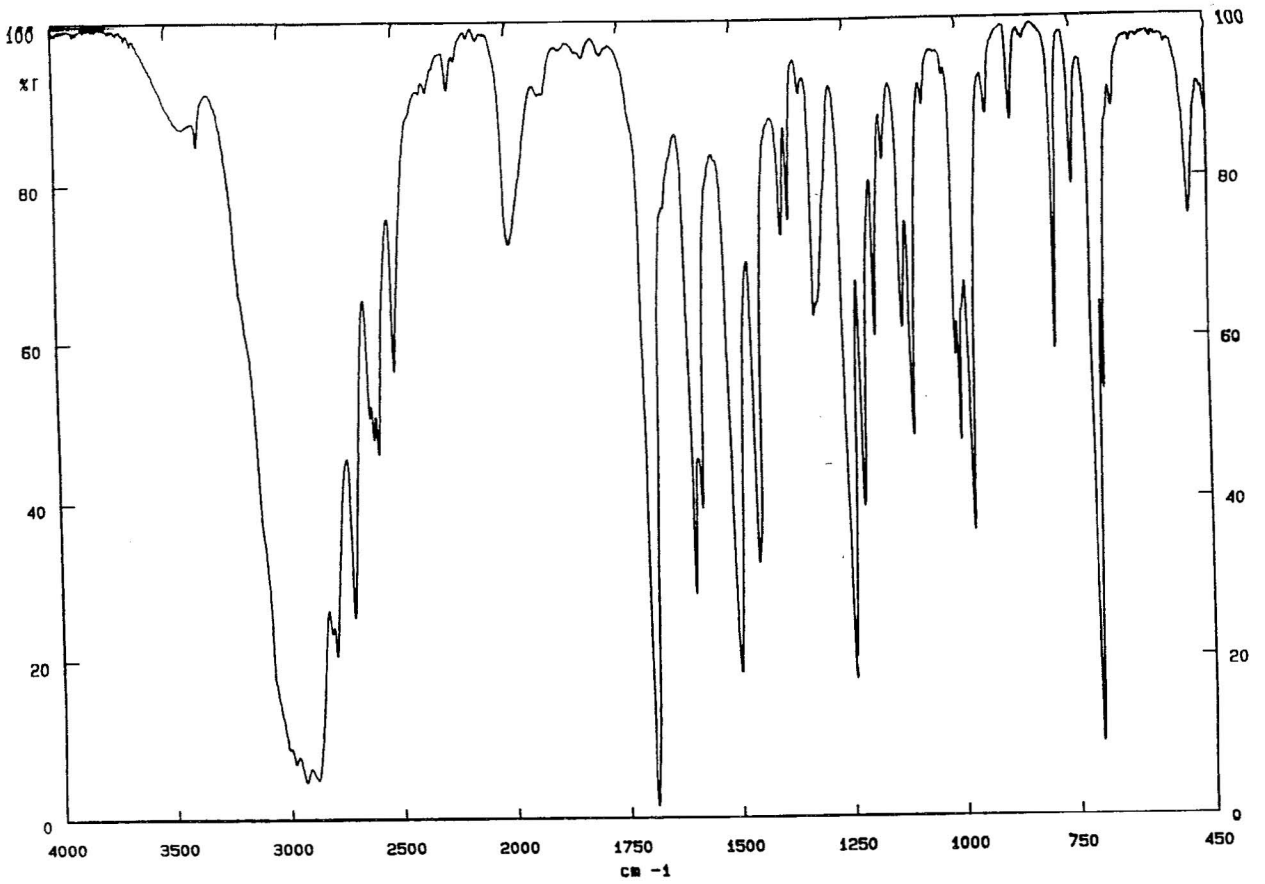


FIGURE 3A - IR SPECTRA CATHINONE HCL

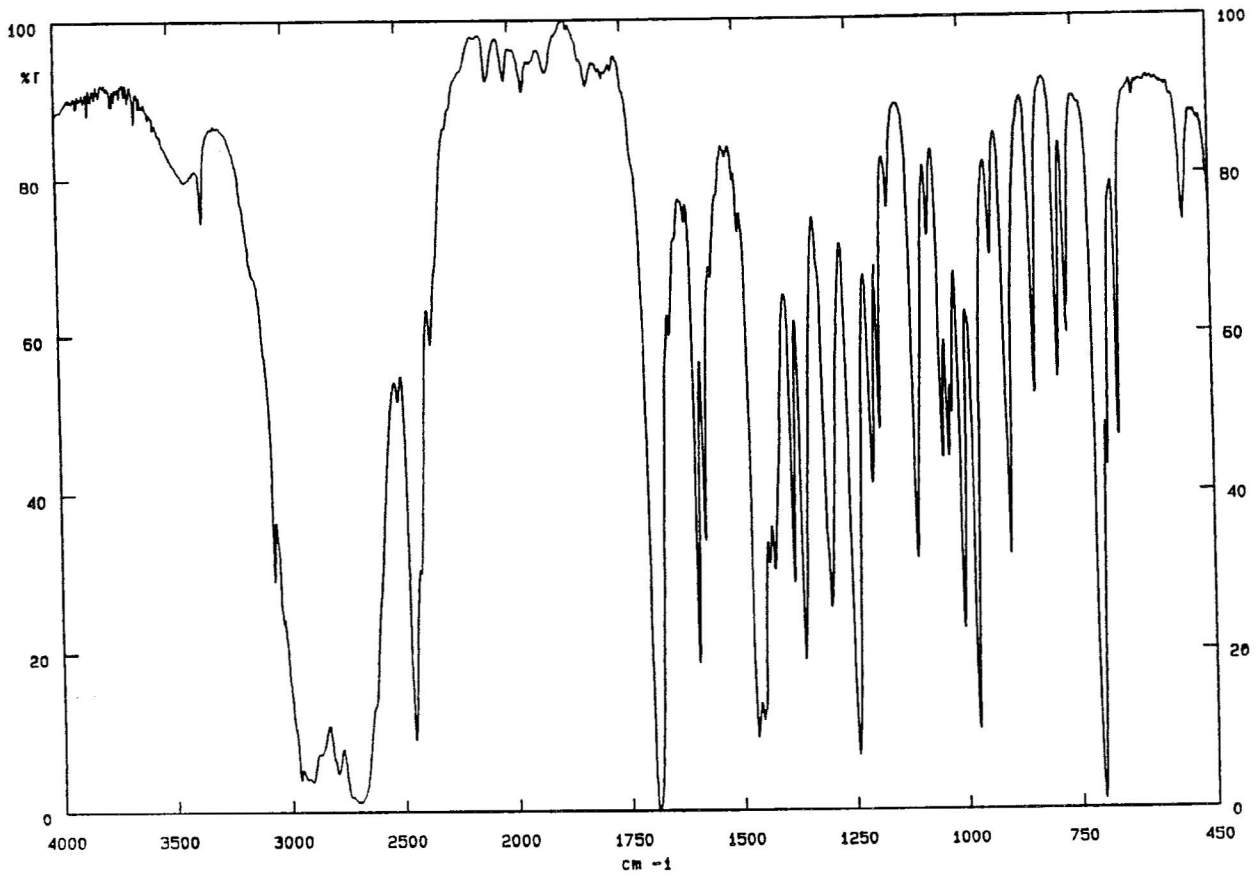
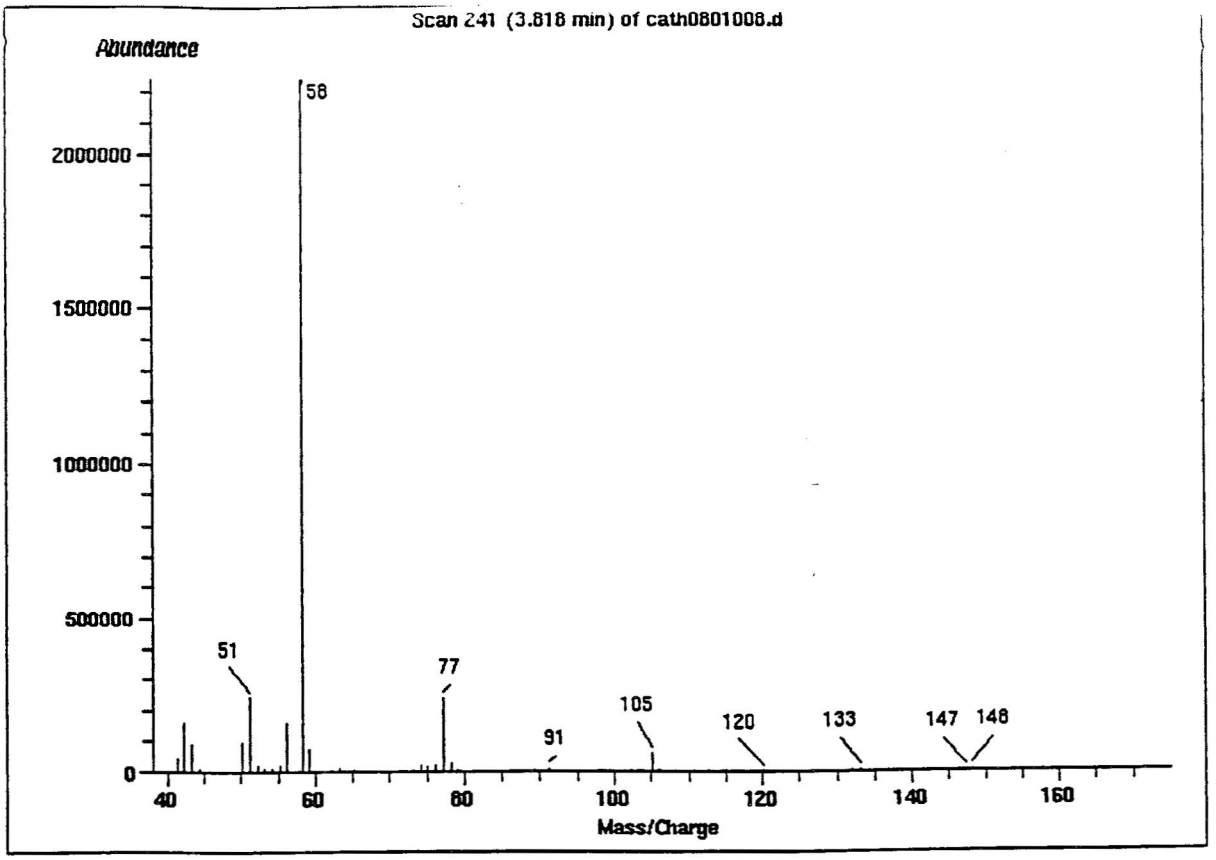
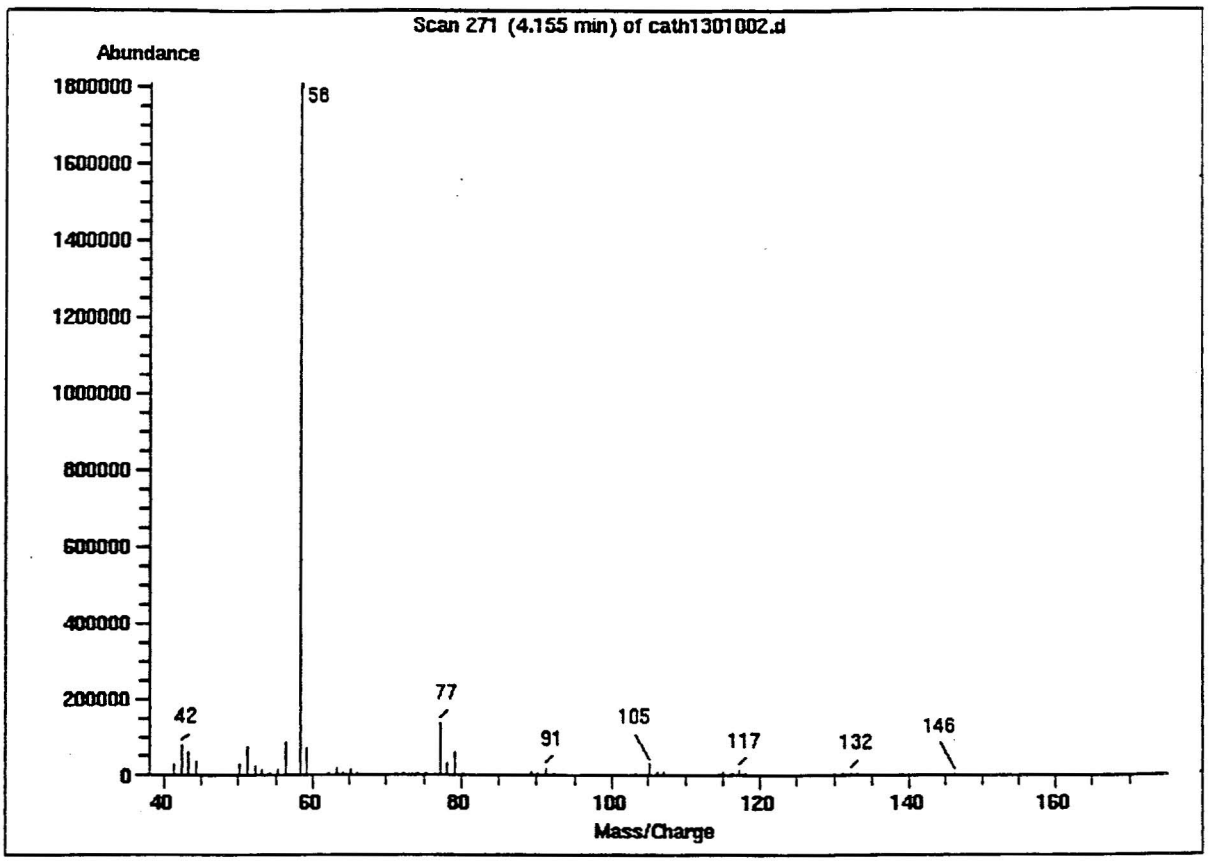


FIGURE 3B - IR SPECTRA METHCATHINONE HCL

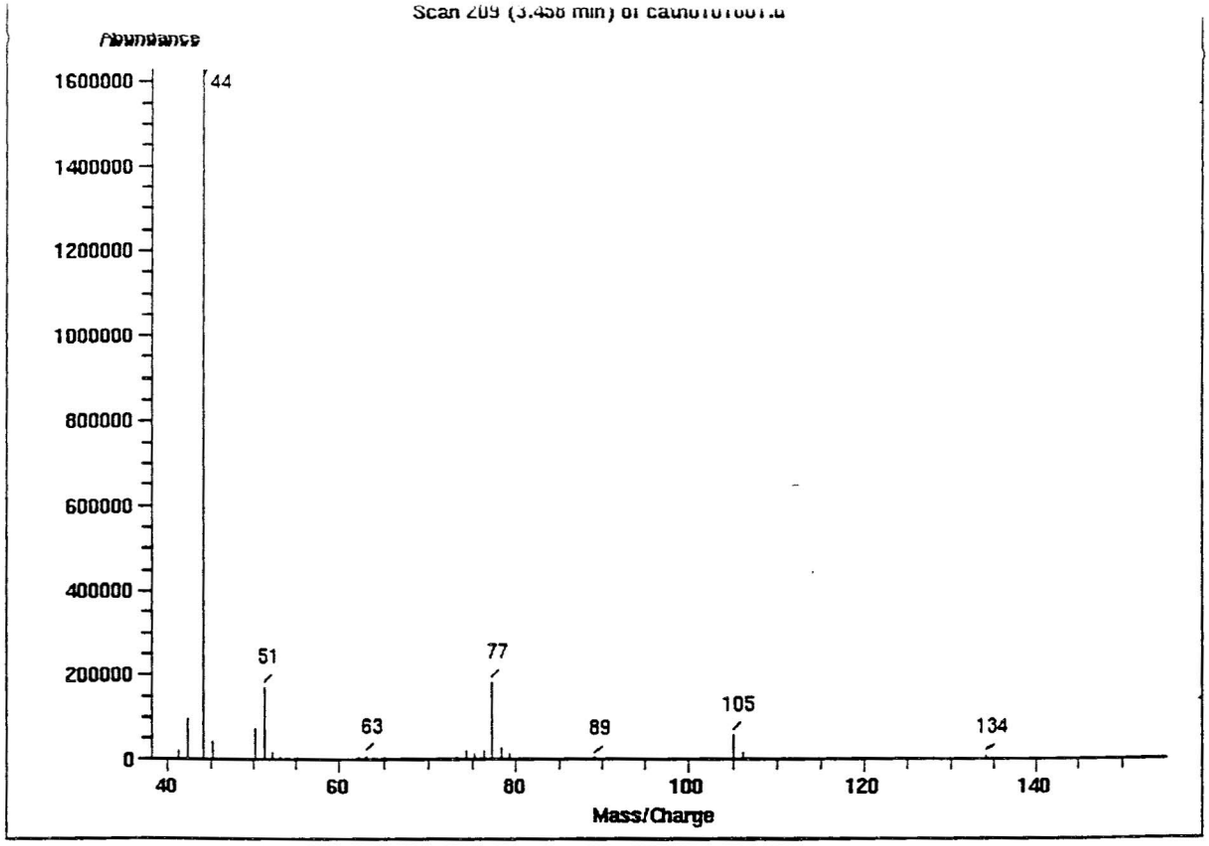


4A-1 methcathinone

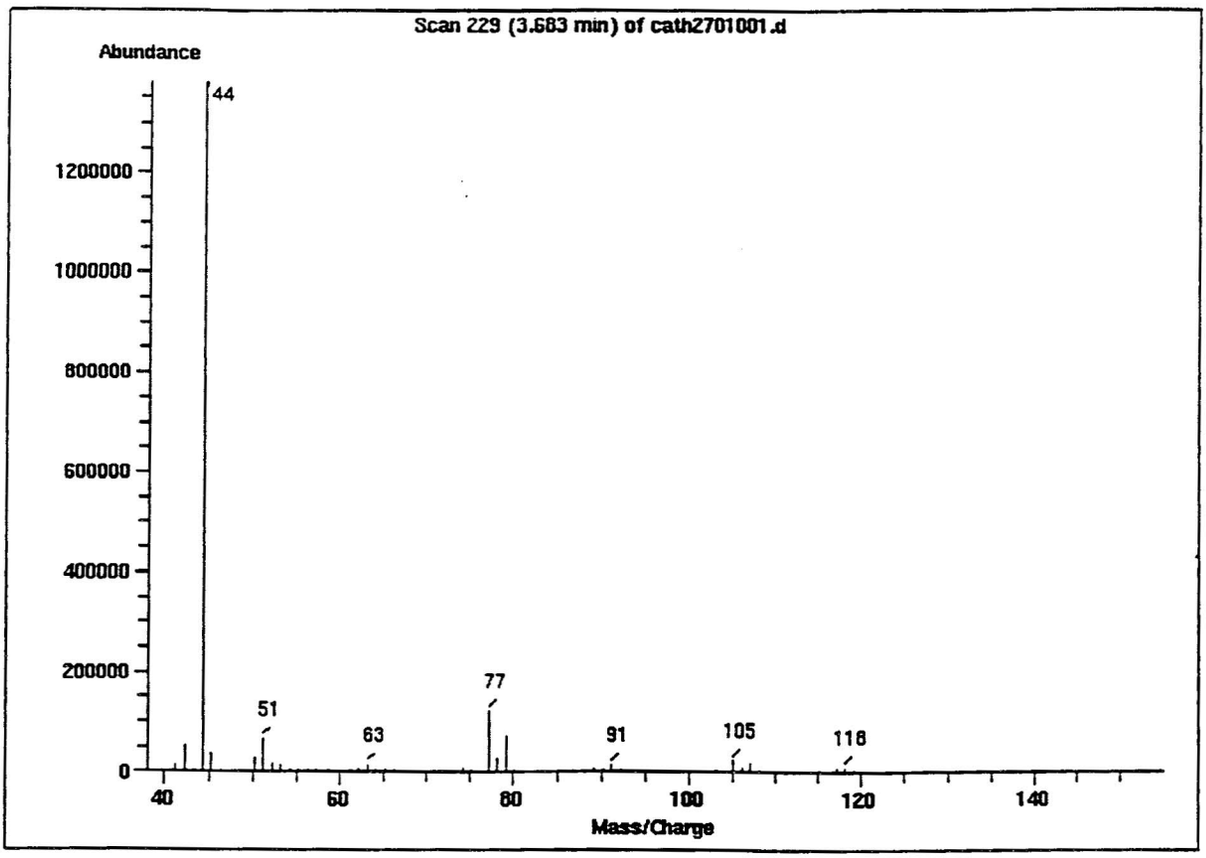


4A-2 ephedrine

FIGURE 4A - MASS SPECTRA OF METHCATHINONE AND SOME RELATED COMPOUNDS

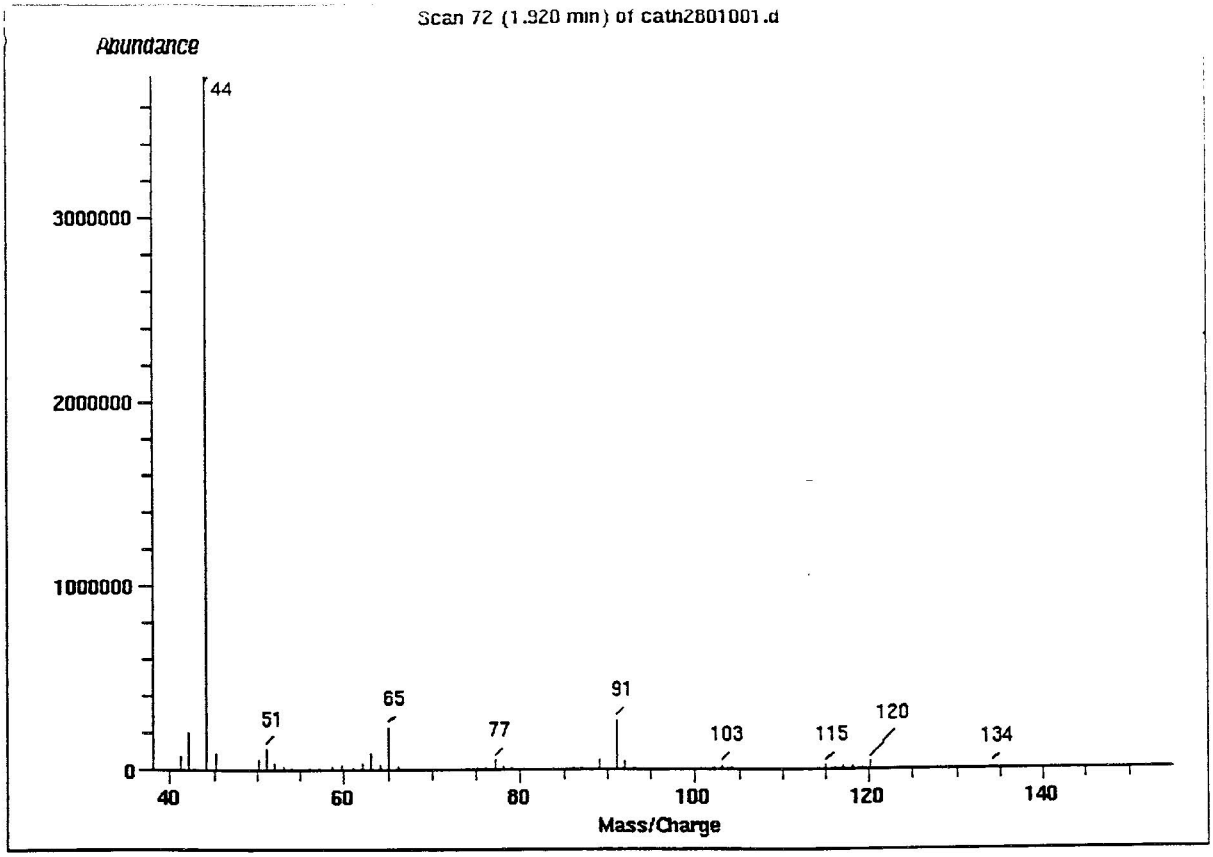


4A-3 cathinone

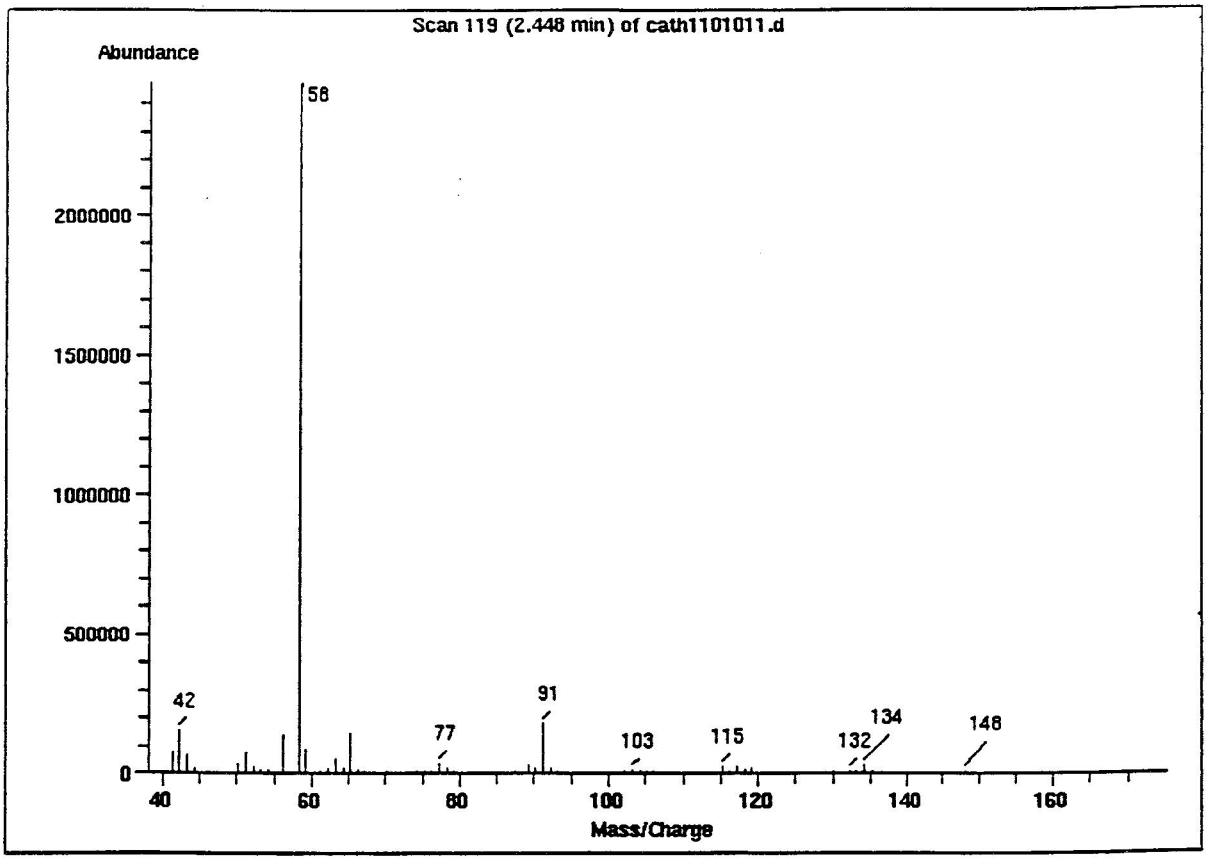


4A-4 norephedrine

FIGURE 4A - MASS SPECTRA OF METHCATHINONE AND SOME RELATED COMPOUNDS

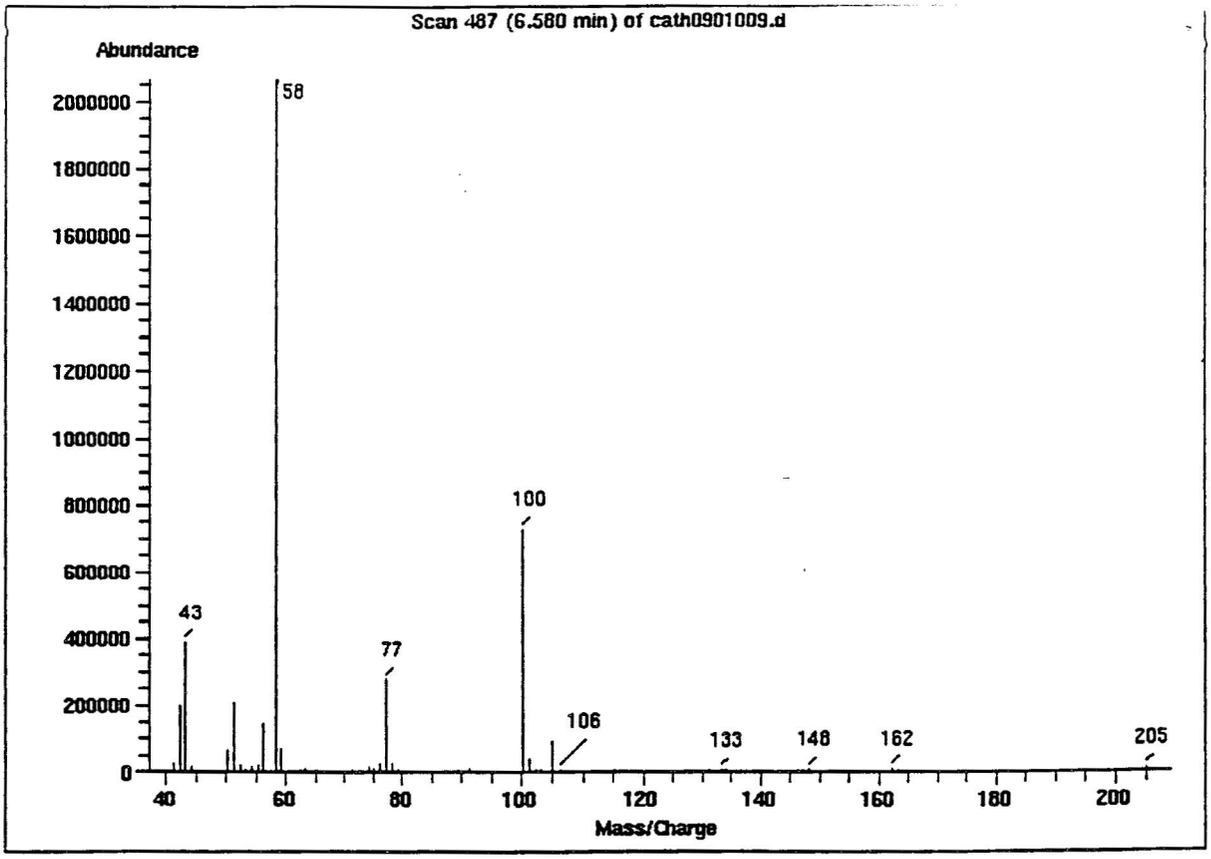


4A-5 amphetamine

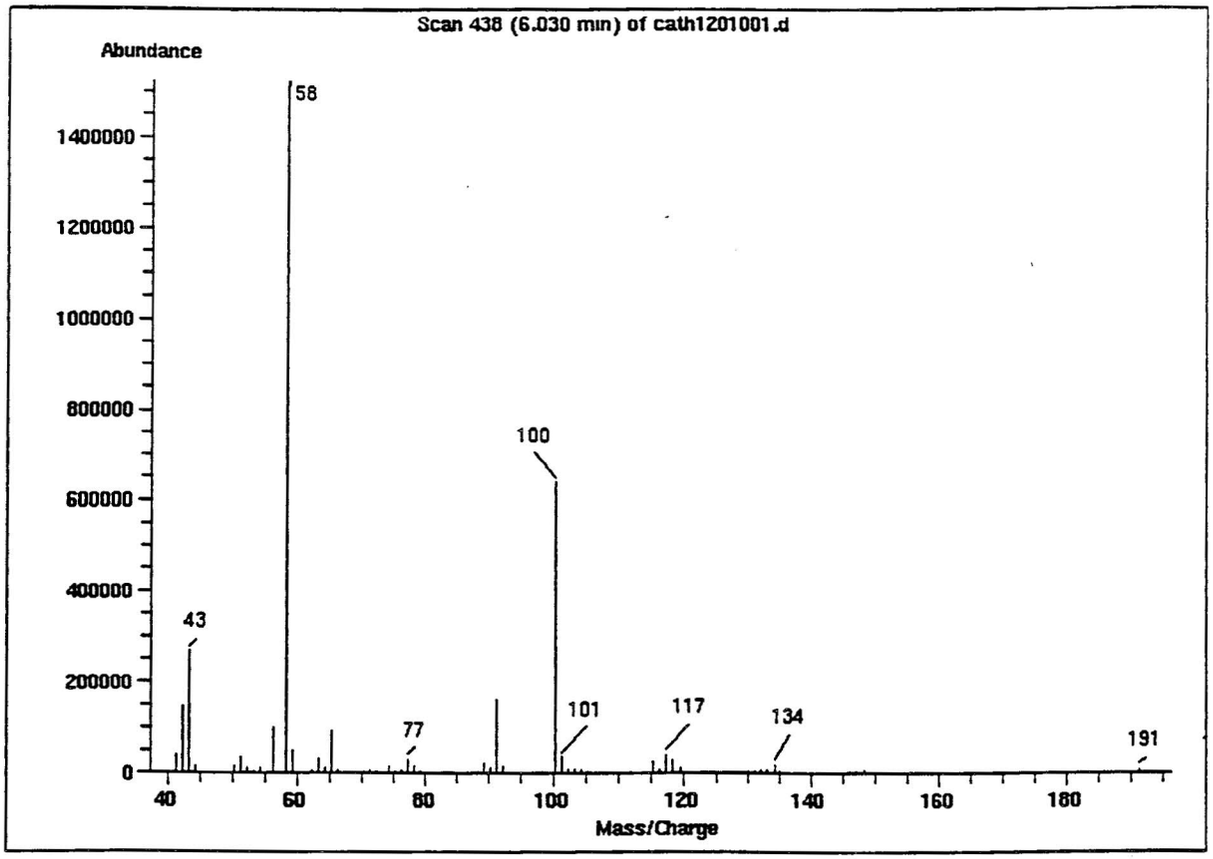


4A-6 methamphetamine

FIGURE 4A - MASS SPECTRA OF METHCATHINONE AND SOME RELATED COMPOUNDS

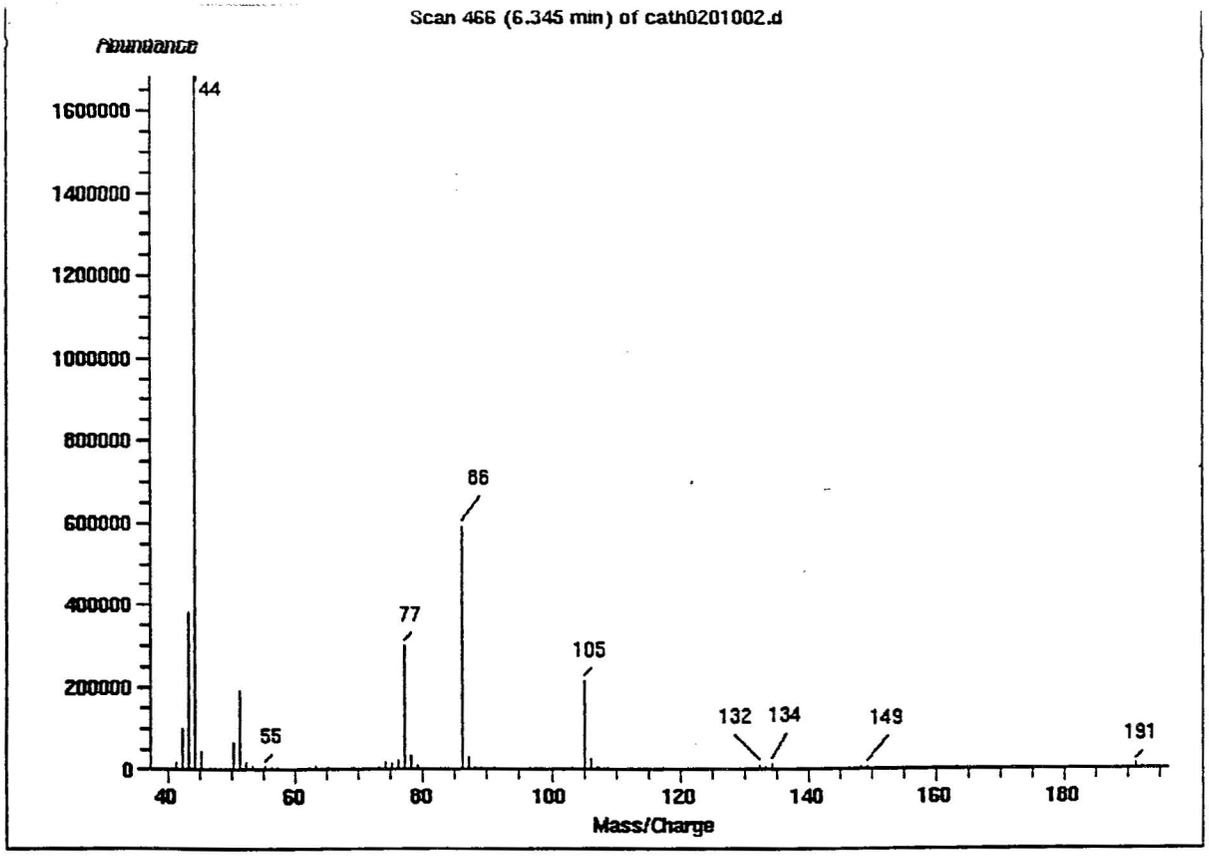


4B-1 acetylmethcathinone

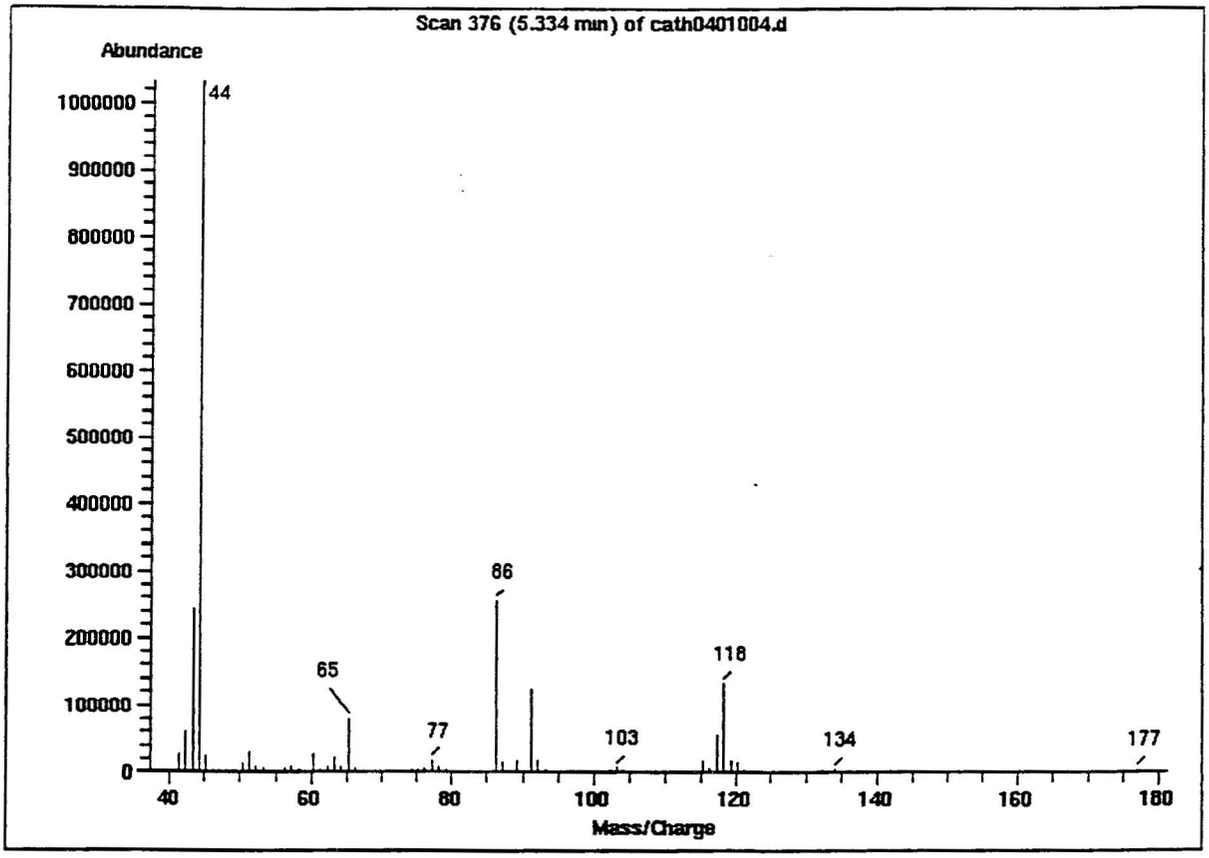


4B-2 acetylmethamphetamine

FIGURE 4B - MASS SPECTRA OF ACETYLMETHCATHINONE AND SOME RELATED COMPOUNDS

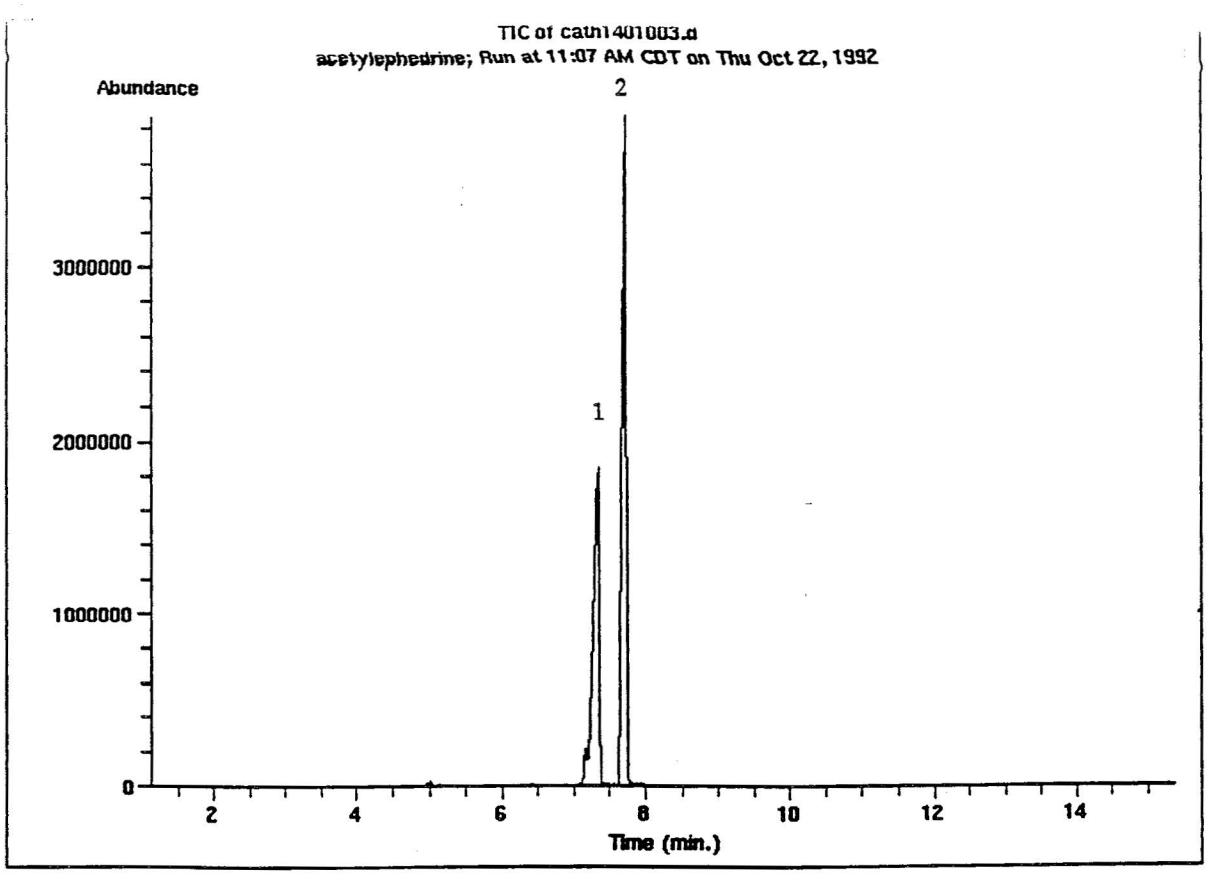


4B-3 acetylcathinone

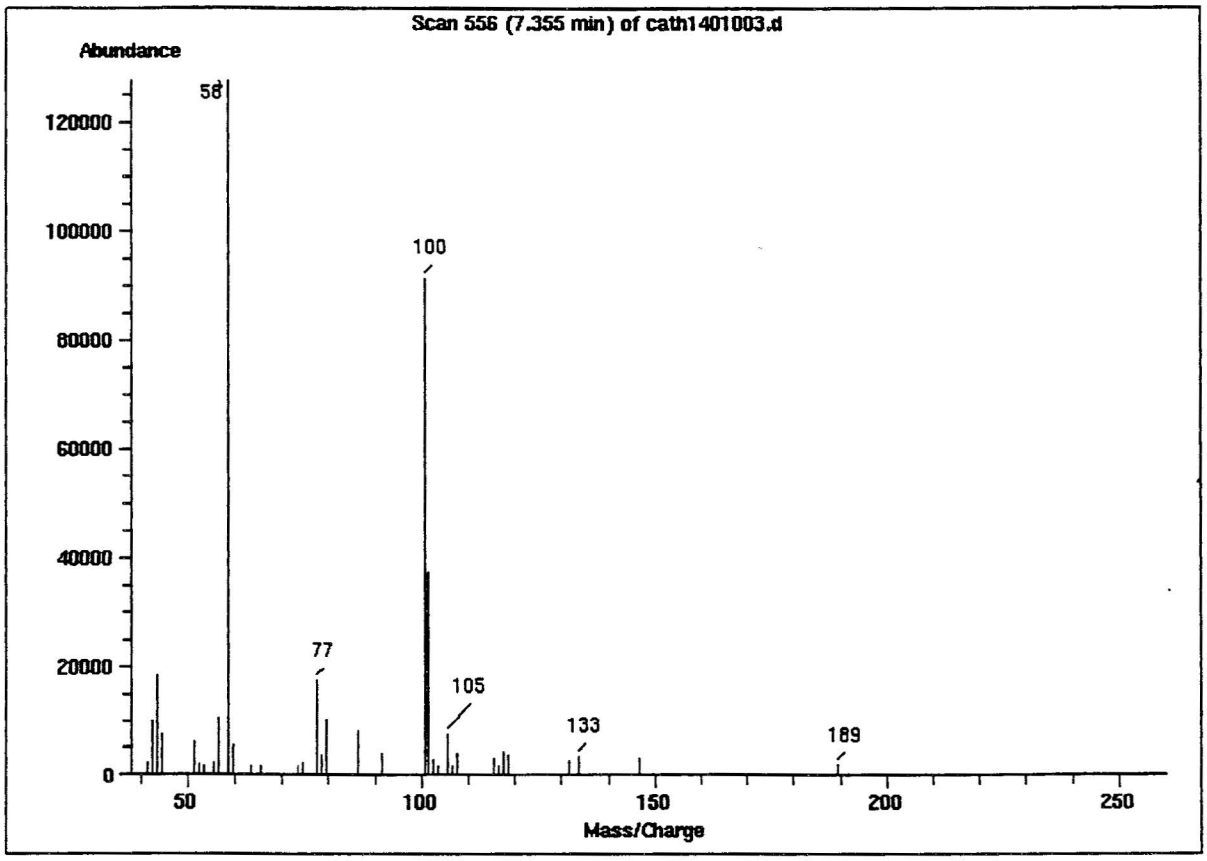


4B-4 acetylamphetamine

FIGURE 4B - MASS SPECTRA OF ACETYLMETHCATHINONE AND SOME RELATED COMPOUNDS

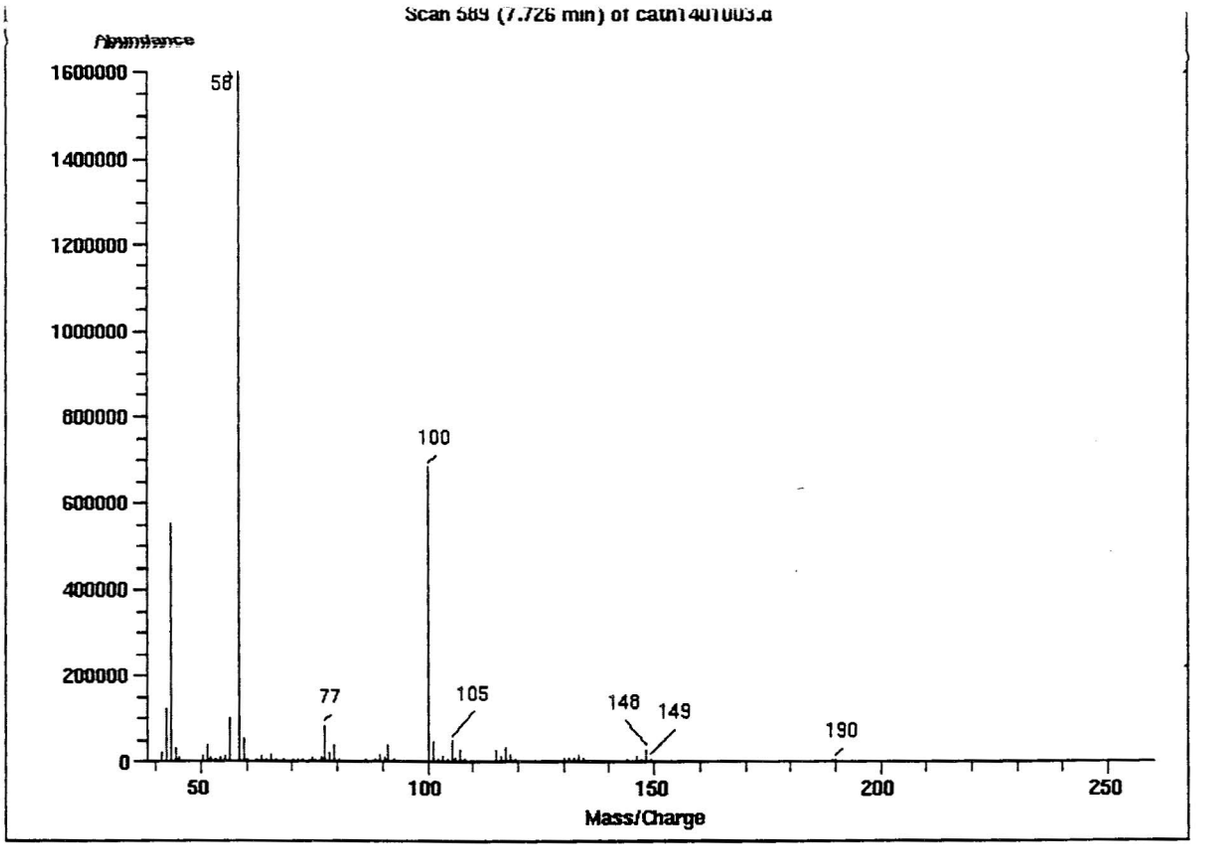


4B-5 TIC of acetylated ephedrine

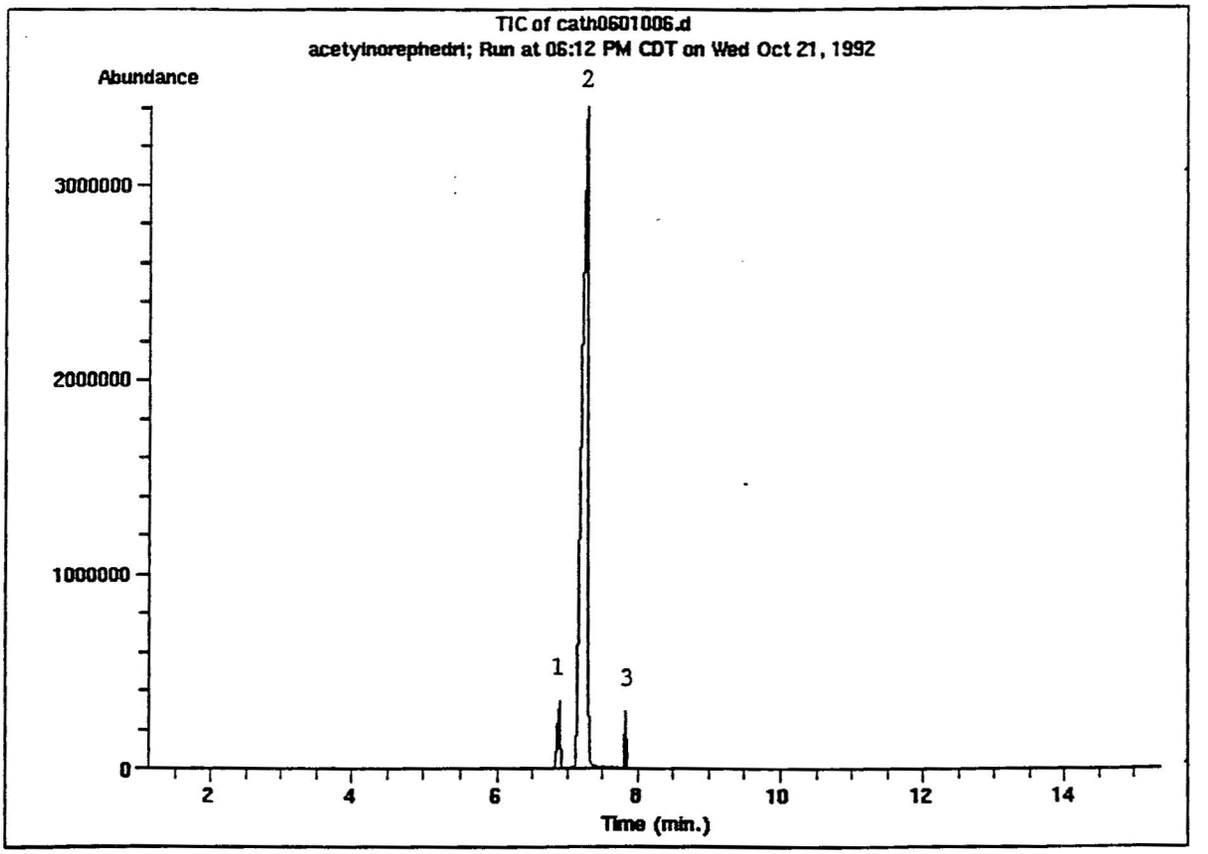


4B-6 acetylated ephedrine peak 1

FIGURE 4B - MASS SPECTRA OF ACETYLMETHCATHINONE AND SOME RELATED COMPOUNDS

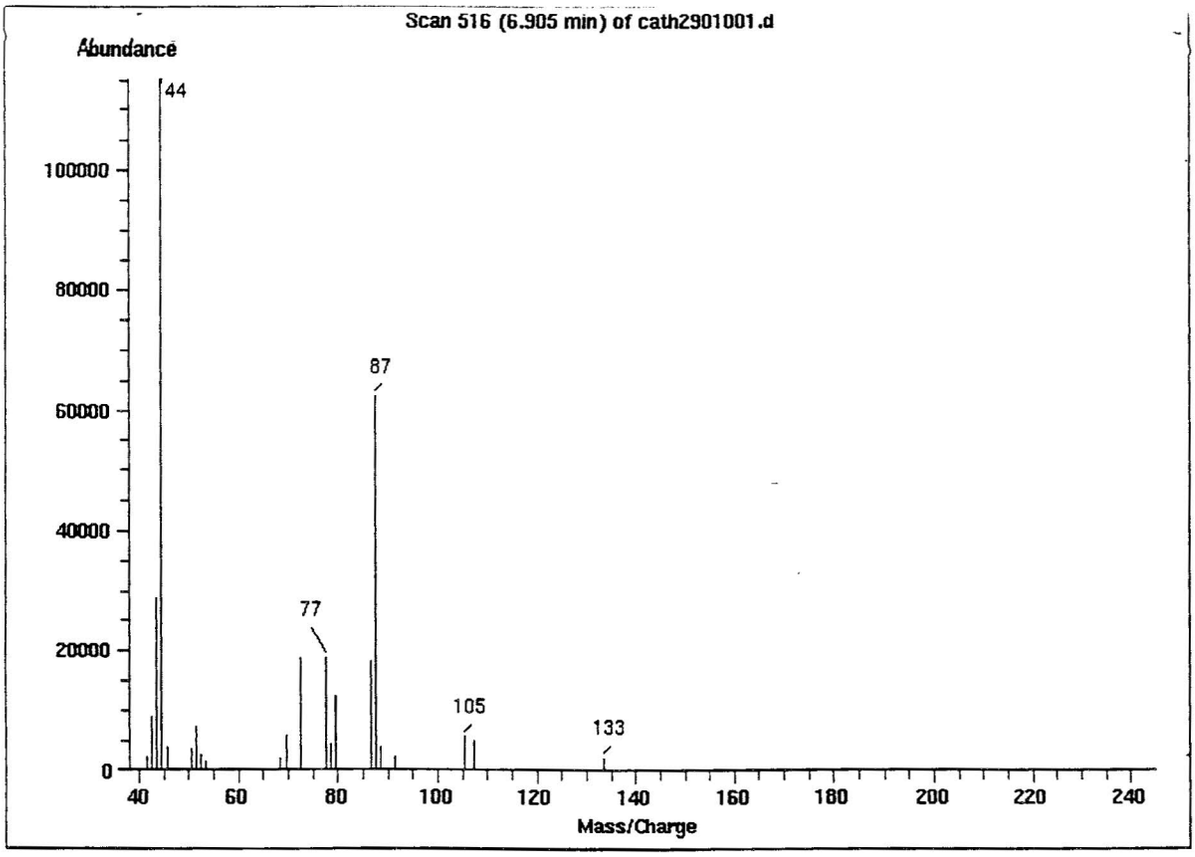


4B-7 acetylated ephedrine peak 2

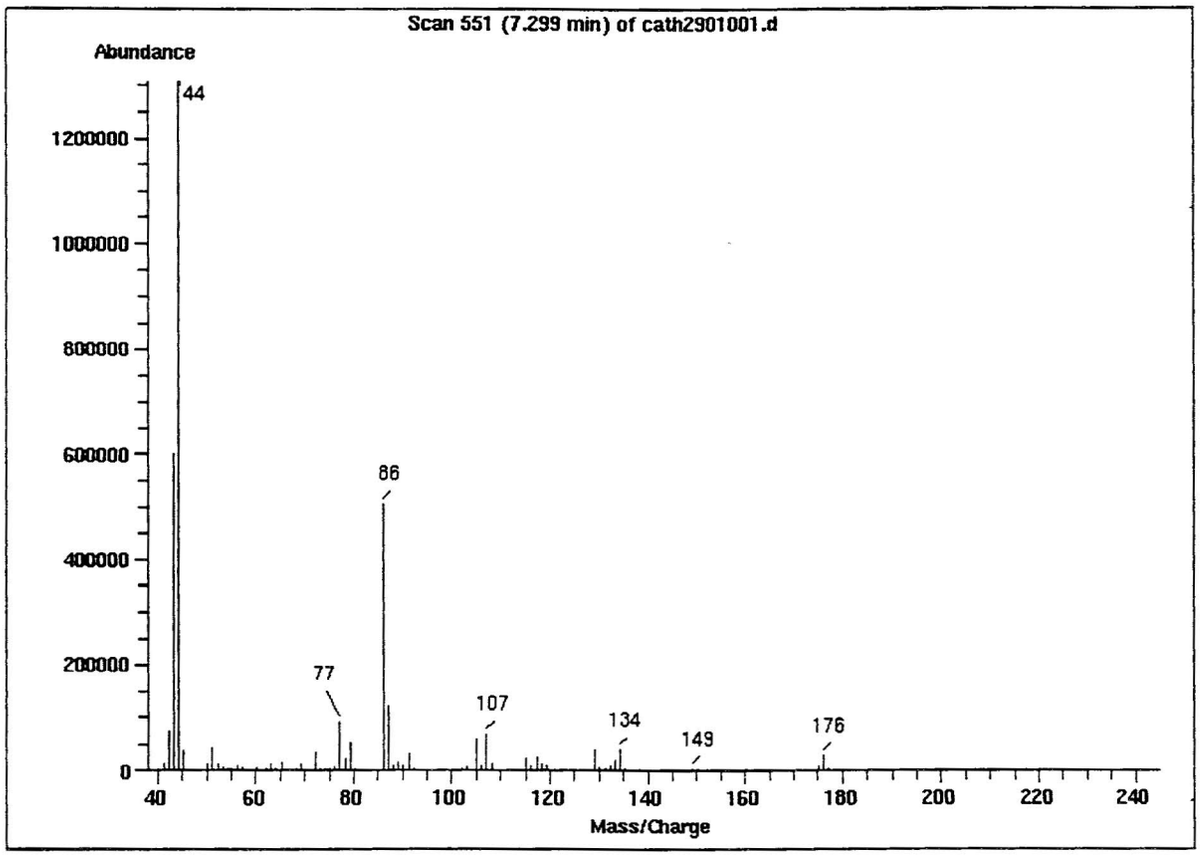


4B-8 TIC of acetylated norephedrine

FIGURE 4B - MASS SPECTRA OF ACETYLMETHCATHINONE AND SOME RELATED COMPOUNDS

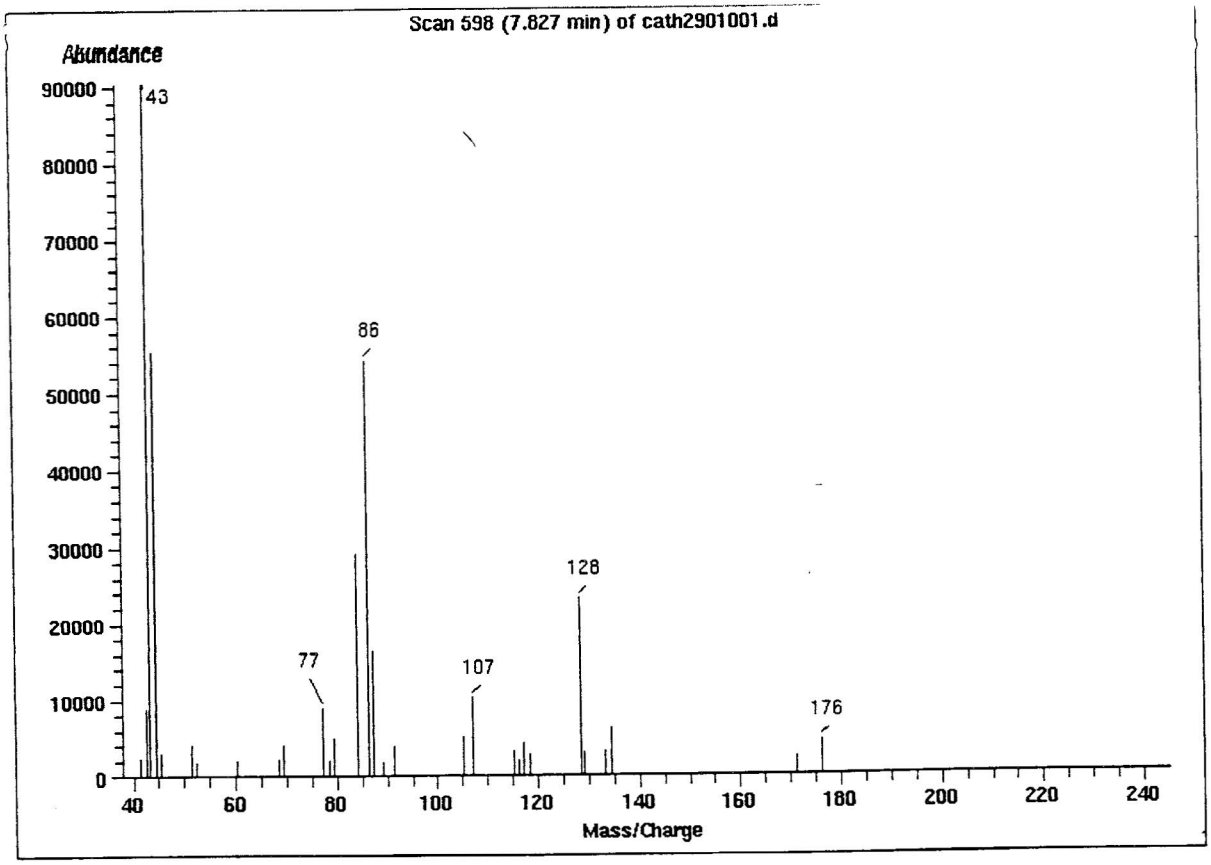


4B-9 acetylated norephedrine peak 1



4B-10 acetylated norephedrine peak 2

FIGURE 4B - MASS SPECTRA OF ACETYLMETHCATHINONE AND SOME RELATED COMPOUNDS



4B-11 acetylated norephedrine peak 3

FIGURE 4B - MASS SPECTRA OF ACETYLMETHCATHINONE AND SOME RELATED COMPOUNDS