Synthesis and Identification of N,N-Dimethylcathinone Hydrochloride

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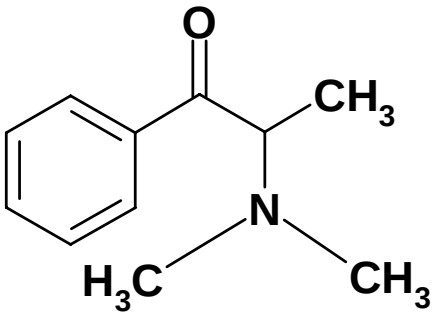
ABSTRACT: The syntheses and analyses of N,N-dimethylcathinone and N-ethylcathinone are presented and discussed.

KEYWORDS: N,N-Dimethylcathinone, N-Ethylcathinone, α-Aminopropiophenones, Synthesis, Analysis, Forensic Chemistry



Dimethylcathinone

Introduction

Although substantial information has been published concerning the analysis and identification of cathinone (2-amino-1-phenyl-1-propanone, α-aminopropiophenone)[a] and methcathinone (2-methylamino-1-phenyl-1-propanone, α-methylaminopropiophenone) [1-6], very little analytical data has been published to assist in the identification of the structural analog N,N-dimethylcathinone hydrochloride (hereafter "dimethylcathinone").[b] A recent seizure of a very large quantity of this drug [7] has spurred interest in its analysis.

While various synthetic aminopropiophenones are popular drugs of abuse in Europe [8,9], with the minor exceptions of methcathinone and methylone (N-methyl-3,4-methylenedioxypropiophenone) [10], this interest has not been matched in the United States (U.S.). The abuse of khat (*Catha edulis*), which contains small amounts of

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[a] "Natural" cathinone (from khat (*Catha edulis*)) is the S enantiomer; however, in order to avoid confusion, "cathinone" is understood to be a generic (common) term for 2-amino-1-phenyl-1-propanone, and the stereochemistry (R, S, or R/S) is specified as appropriate.

[b] *Editor's Note*: Dimethylcathinone is occasionally referred to as "dimethcathinone" (a now superceded common name). Dimethylcathinone is the proper nomenclature.

(2S)-(-)-cathinone [4,11-16], has been endemic in the east African communities within the U.S., but cathinone is virtually never encountered as a clandestinely synthesized or extracted drug, possibly because of its instability in free base form. Under U.S. law, cathinone, khat, and methcathinone are all Schedule I Controlled Substances. Currently (early 2008), dimethylcathinone is not scheduled; however, prosecution of this compound (as a Schedule I drug) would be conducted under the tenets of the Controlled Substances Analogue Enforcement Act.

Quite surprisingly, racemic dimethylcathinone is approximately equipotent with both racemic cathinone and racemic amphetamine, while the (2S)-(-)-enantiomer is nearly equipotent with both (2S)-(-)-cathinone and (2S)-(+)-amphetamine [17,18]. This is in direct contrast with (2S)-(+)-dimethylamphetamine, which has been found in drug discrimination studies to be only approximately one tenth as potent an analeptic agent (CNS stimulant) as (2S)-(+)-amphetamine [17]. This unexpected potency likely explains the recent appearances of dimethylcathinone in clandestine markets.

(2S)-(-)-Dimethylcathinone can be synthesized from (1R,2S)-(-)-N-methylephedrine by oxidation with potassium permanganate [5,19,20] or any of a variety of chromium compounds, most often sodium or potassium dichromate [21-27]. Alternatively, racemic dimethylcathinone can be prepared from 2-bromopropiophenone by reacting with dimethylamine [17,28-32]. Herein, the synthesis and analysis of dimethylcathinone are presented and discussed. For comparative purposes, analytical data for N-ethylcathinone (hereafter "ethylcathinone"), an isomeric structural analog of dimethylcathinone, are also presented.

Experimental

Instrumentation: Solid state Fourier Transform infrared (FTIR) spectra were acquired as a potassium bromide matrix, with a Thermo Nicolet Model 6700 Fourier Transform Infrared Spectrophotometer. Gas phase infrared (IRD) spectra were obtained using a Bio-Rad (now ASAP) IRD II infrared detector interfaced to an Agilent 6890 Gas Chromatograph (GC) with an HP-5 30 m x 0.32 mm x 0.25 m column in splitless mode from 80^0C (2.0 min) at 15^0C/min to 270^0C (2.0 min). Mass spectra were acquired using an Agilent 5973 Mass Selective Detector (MSD) attached to an Agilent 6890 GC. This GC had the same type column as above but used a program from 80^0C (2.0 min) at 20^0C/min to 240^0C (0.5 min) in split mode (100:1). Nuclear magnetic resonance (NMR) spectra were acquired at 400 MHz using a Varian Mercury 400 NMR. The compounds were analyzed as the hydrochloride salts in deuterium oxide (D_2O). Melting points were determined with a Thomas-Hoover "Unimelt" apparatus. Polarimetry on the (2S)-(-)-dimethylcathinone HCl was performed using a Perkin-Elmer Model 241 Polarimeter with a 10 cm (1 decimeter) sample cell. All data were acquired at the DEA North Central Laboratory with the exception of the NMR spectra, which were provided by the DEA Special Testing and Research Laboratory (Dulles, VA).

Syntheses and Melting Points: Racemic dimethylcathinone and racemic ethylcathinone were prepared by reacting 2-bromopropiophenone (Aldrich Chemical Co., Milwaukee, WI) with dimethylamine or ethylamine, respectively, as aqueous free bases at -8^0C (ice-salt bath). (2S)-(-)-Dimethylcathinone HCl was prepared by oxidizing (1R,2S)-(-)-N-methylephedrine HCl (Aldrich) with a sodium dichromate/sulfuric acid solution at -5^0C (ice-salt bath). The hydrochloride salts of all compounds were prepared by the addition of a 5% isopropanol/HCl solution to a chloroform solution of the respective free base.

Racemic dimethylcathinone HCl, mp = 206-206.5^{0}C
Racemic ethylcathinone HCl, mp = 186-188^{0}C
(2S)-(-)-Dimethylcathinone HCl, mp = 197.5-200^{0}C, $[\alpha] = -52.5^O$ (H_2O, 1%), T = 21^0C

Gas Chromatography - Mass Spectrometry (GC/MS): The mass spectra of dimethylcathinone and ethylcathinone were acquired as the free bases in chloroform, prepared by dissolving the HCl salts in water, adding saturated sodium carbonate, and extracting into chloroform. The resulting extracts were then passed through a disposable pipette containing a pledget of glass wool and into a glass vial, then introduced into the GC/MS. The mass

spectra of N-acetylethylcathinone was acquired by adding acetic anhydride to a solution of ethylcathinone in chloroform, and immediately injecting the mixture into the GC/MS (the acetylation occurs in the injection port).

Infrared Spectroscopy (FTIR): The two compounds were analyzed as the hydrochloride salts in a compressed potassium bromide matrix.

Infrared Spectroscopy (IRD): The two compounds were introduced to the IRD as free bases in chloroform through an Agilent 6890 GC.

NMR Spectrometry: The 400 MHz proton NMR spectra were acquired by the DEA Special Testing and Research Laboratory (Dulles, VA). Maleic acid was used as an internal standard (peak at 6.40 ppm). Hydrogen exchange with the D_2O solvent is responsible for the HOD resonance at 4.80 ppm. The 0.00 ppm reference peak is from 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt, present in the D_2O solvent (Aldrich).

Color Tests: Although ethylcathinone HCl is a secondary amine, its response to the secondary amine test is almost imperceptible, with only a slight bluish ring forming in a porcelain spot plate after a short period of time. Both of the cathinone analogs give a dull orange with Chen's reagent. Ethylcathinone starts to respond to the reagent in about 90 seconds, while dimethylcathinone starts to respond in about 180 seconds. Full dissipation of the initial "Robin's Egg Blue" color of the reagent mixture requires 10 minutes or more, giving an orange-brown color. Preparation of the reagents is given in Reference 1.

Results and Discussion

The GC retention times of dimethylcathinone and ethylcathinone are very close using the column and parameters specified in the Instrumentation section (dimethylcathinone 7.07 min; ethylcathinone 7.19 min). The resulting mass spectra are typical of simple phenethylamines (Figures 1a-b). The molecular ions are nearly imperceptible, and a large base peak is observed at m/z = 72, indicative of the respective immonium ions. However, ethylcathinone also has a significant ion at m/z = 44, from loss of ethylene from the m/z = 72 ion [33]. This allows easy differentiation of the two compounds, a distinction that is further enhanced by conversion of ethylcathinone to N-acetylethylcathinone with acetic anhydride. N-Acetylethylcathinone gives a mass spectrum having a very large ion at m/z = 114 (72 + 42) and a small molecular ion at m/z = 219 (177 +42) (Figure 1c). Dimethylcathinone (a tertiary amine) does not react with acetic anhydride. A detailed elucidation of the fragmentation patterns for methamphetamine and related compounds has recently been published [34].

Although GC/MS is the method of choice for identification of many compounds, infrared spectrophotometry may be preferable for dimethylcathinone. The solid state FTIR of a purified sample gives a distinctive spectrum that also allows identification of the salt form (Figures 2a-b). When available, IRD offers the convenience of GC/MS without the sample preparation often required for FTIR. IRD spectra, although lacking the fine structure seen in solid state FTIR spectra, are nonetheless distinct and avoid potential difficulties which may occur with some compounds due to polymorphism (Figures 3a-b).

Proton NMR also gives distinct spectra for dimethylcathinone and ethylcathinone. The spectra are easily distinguished by the resonances for the dimethylamino versus ethylamino groups, between 1.30 and 3.30 ppm (Figures 4a-b).

Color tests (presumptive tests, field tests) are often useful in determining the initial direction of an analysis. In the case of cathinone-based compounds, however, the *beta*-keto group appears to have an adverse effect on several commonly used reagents (e.g., Marquis and secondary amine), by slowing or preventing the color responses typically observed for simple secondary phenethylamines. One test that is somewhat useful is the Chen's Test. When a blank is prepared from the three components comprising the reagent, a "Robin's Egg Blue" precipitate results. This is the initial response of this reagent to the cathinone compounds tested to date. However, when

allowed to sit undisturbed for periods of up to 10 minutes, the blue precipitate dissipates, leaving a clear orange to orange-brown solution. In contrast, the corresponding aminoalcohols typically give an immediate purple response [10].

Melting points are useful in determining if a pure enantiomer or the racemate of dimethylcathinone is present. Enantiomers can be more rigorously identified with polarimetry. However, caution is needed when performing polarimetry on any of the α-aminopropiophenones. Cathinone free base is known to racemize quickly in hydrolytic solvents (methanol, ethanol, etc.), but less rapidly in chloroform or methylene chloride. The propensity for enantiomeric dimethylcathinone to racemize is unknown. The oxalate and hydrochloride salt forms of dimethylcathinone are stable as dry powders.

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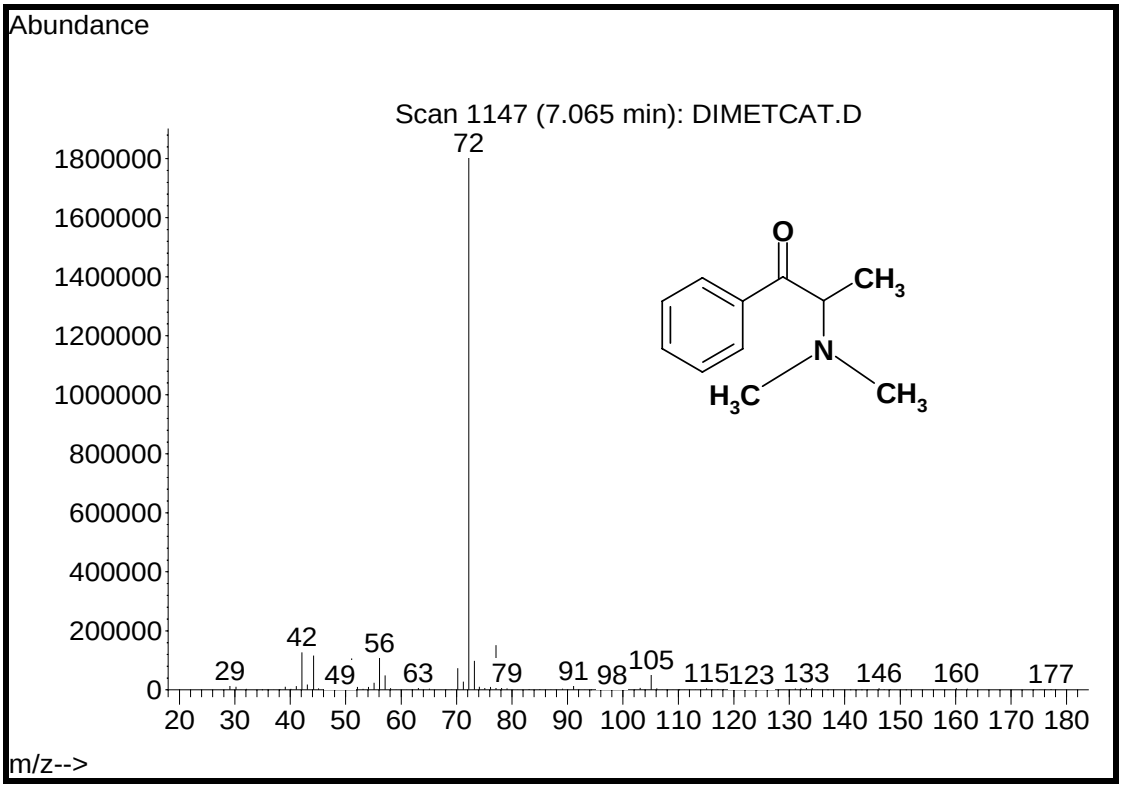

Figure 1a. Mass Spectrum of Dimethylcathinone.

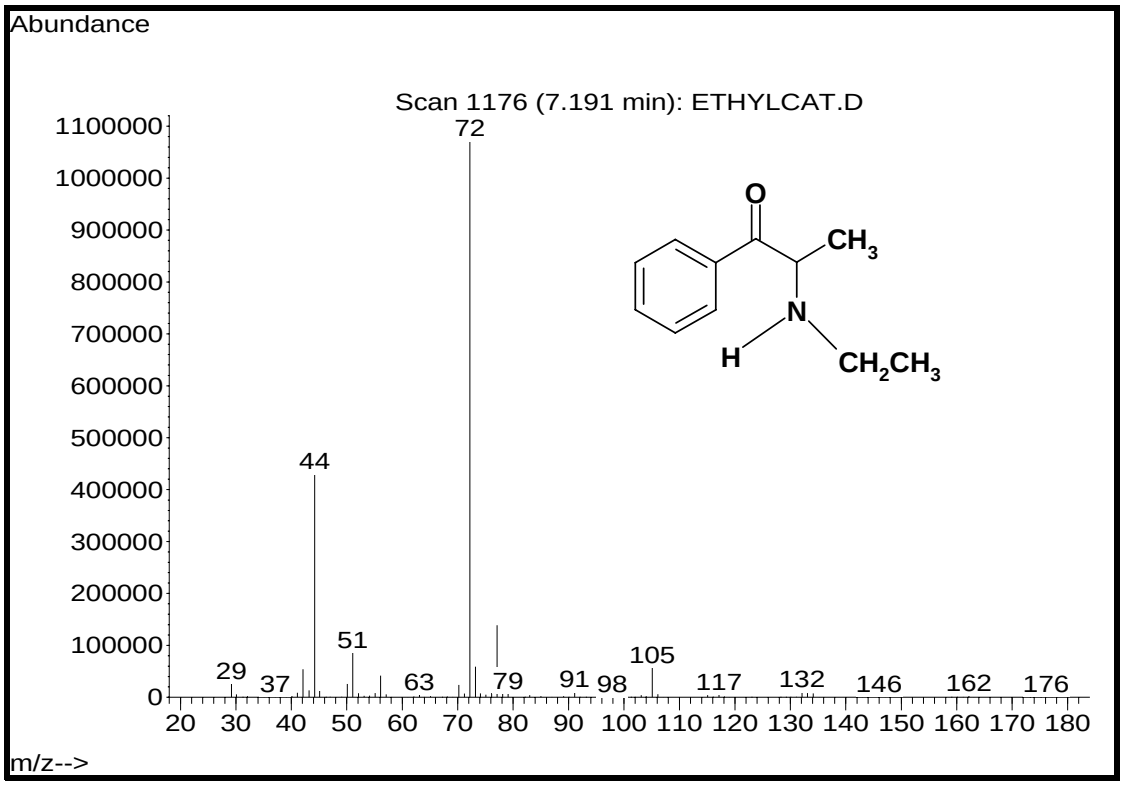

Figure 1b. Mass Spectrum of Ethylcathinone.

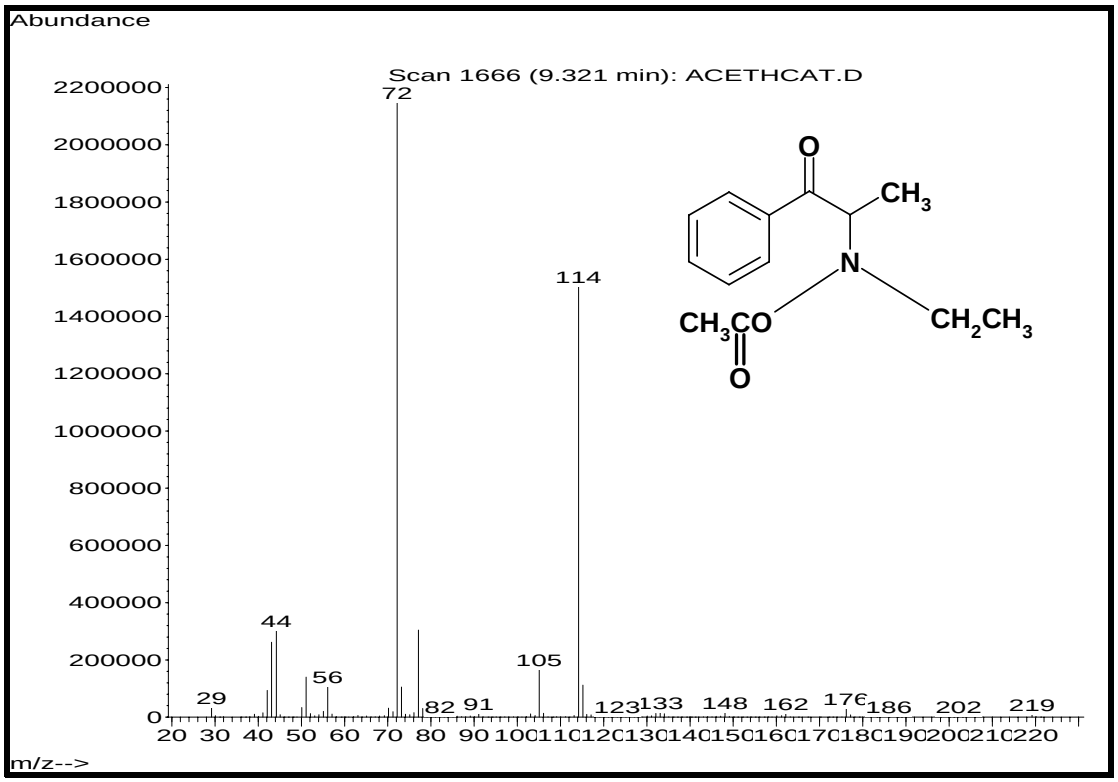

Figure 1c. Mass Spectrum of N-Acetylethylcathinone.

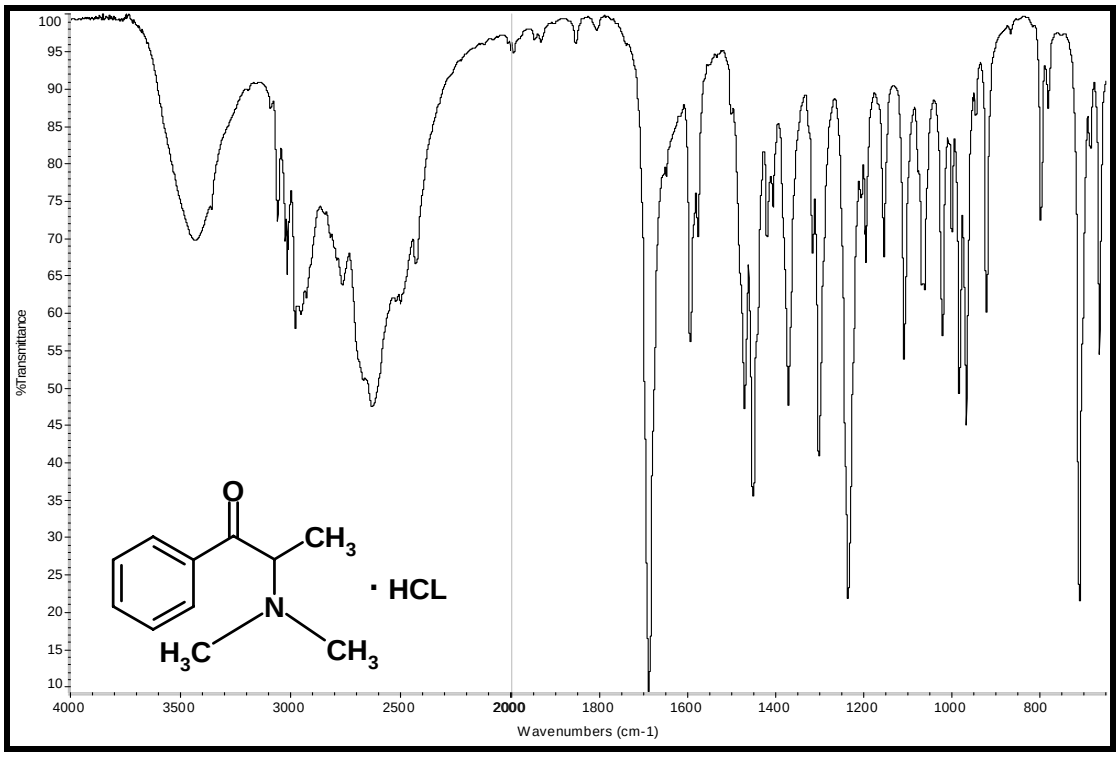

Figure 2a. FTIR of Dimethylcathinone HCl.

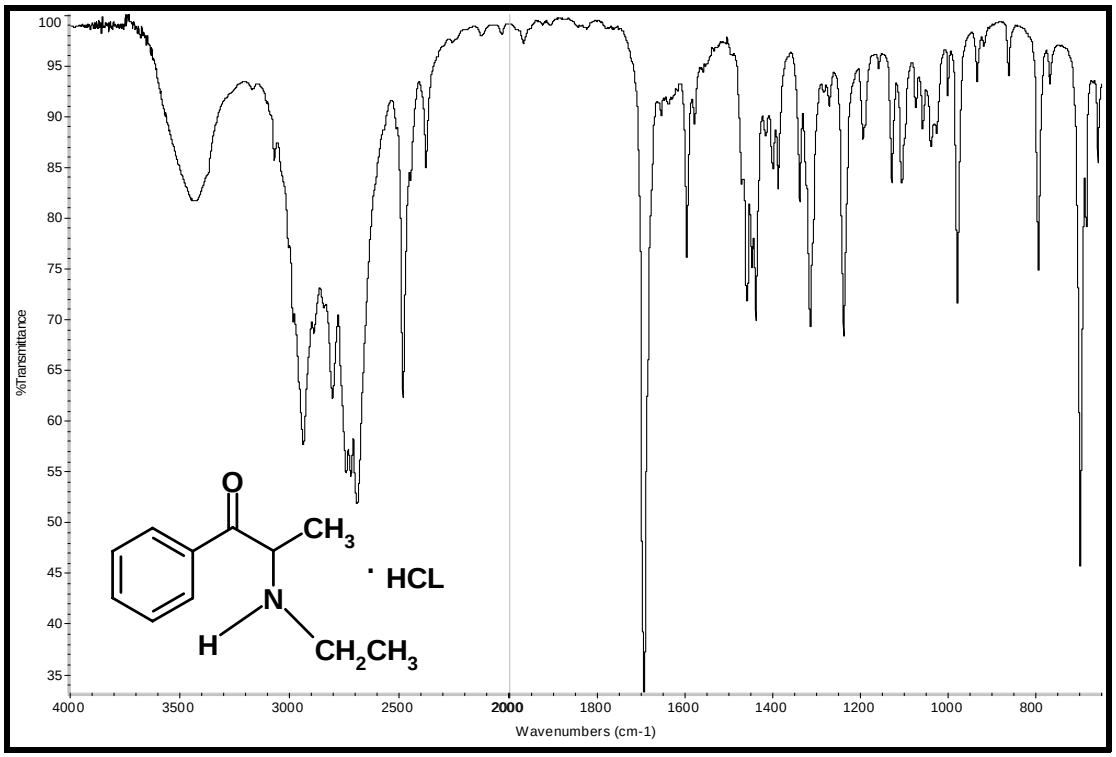

Figure 2b. FTIR of Ethylcathinone HCl.

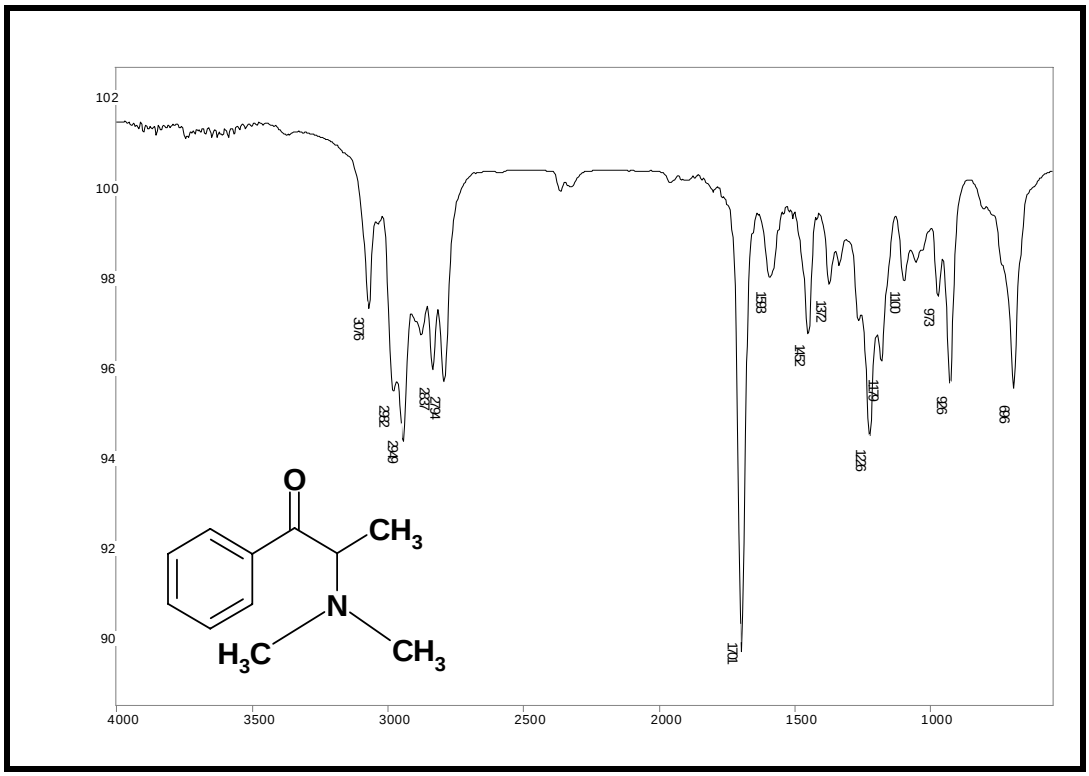

Figure 3a. IRD of Dimethylcathinone.

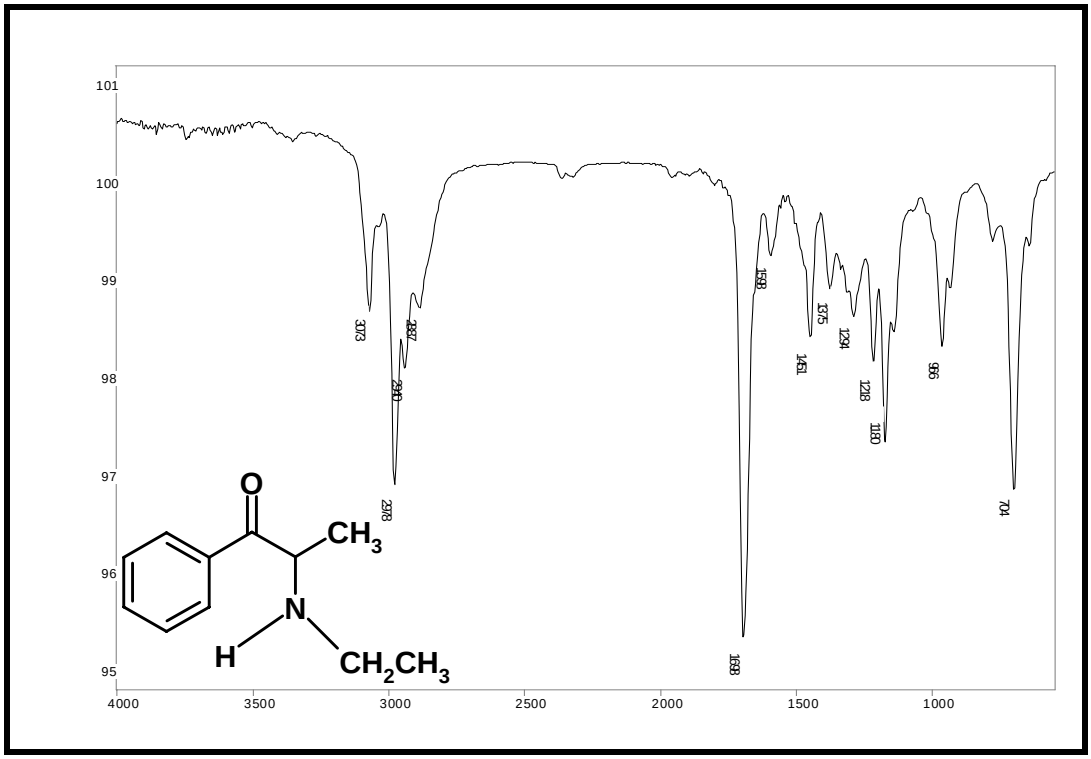

Figure 3b. IRD of Ethylcathinone.

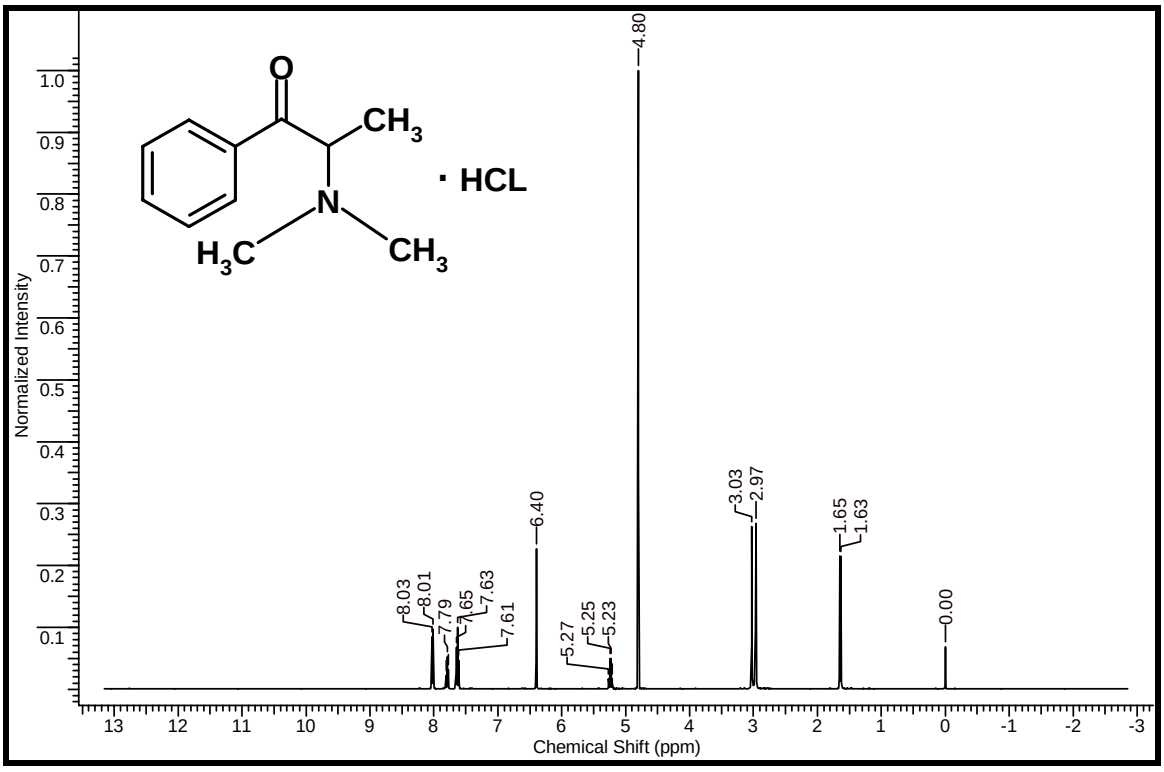

Figure 4a. 400 MHz Proton NMR of Dimethylcathinone HCl in D_2O.

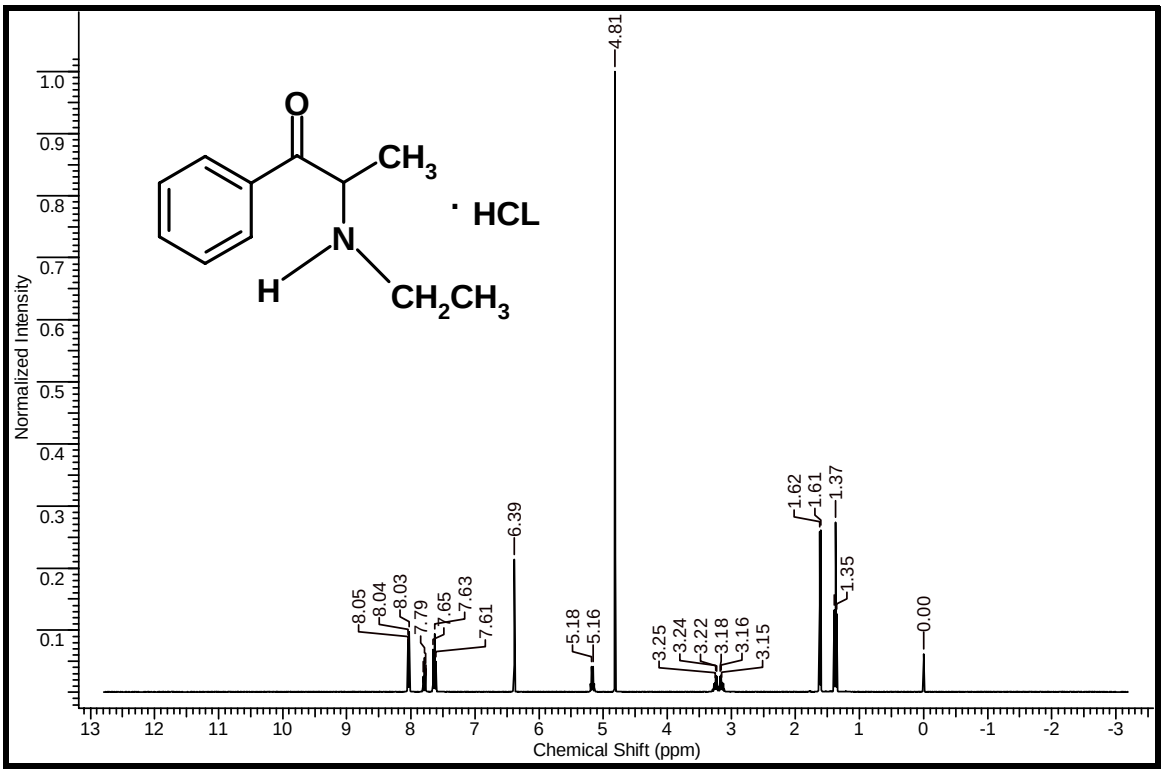

Figure 4b. 400 MHz Proton NMR of Ethylcathinone HCl in D_2O.