The Characterization of 2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexanone (Methoxetamine)

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ABSTRACT: The analysis, characterization, and synthesis of 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (commonly referred to as methoxetamine, "MXE," or "3-Me-O-2-Oxo-PCE") are discussed. Analytical data (nuclear magnetic resonance spectroscopy, mass spectrometry, and infrared spectroscopy) are presented and compared to the structurally similar drug ketamine.

KEYWORDS: 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone, methoxetamine, MXE, 3-Me-O-2-Oxo-PCE, designer drug, synthesis, characterization, forensic chemistry.

The DEA Special Testing and Research Laboratory received a request to characterize an unknown compound in a suspected drug exhibit from another forensic drug laboratory. The exhibit consisted of approximately 200 milligrams of a white powder seized in the northeastern United States. The infrared spectrum of the exhibit was markedly similar to ketamine HCl. However, its mass spectrum differed from ketamine by +10 Daltons (apparent molecular weight of 247 *vs*. 237 for ketamine), including a base peak of +10 Daltons greater than that of ketamine. Additionally, the chlorine isotope pattern found in ketamine was not present. A mass spectral library search using the 2011 Wiley Designer Drug Library resulted in no matches. We suspected that the compound might be methoxetamine (based on the mass spectral data) and obtained 100 milligrams of sample for structural elucidation at our laboratory.

Methoxetamine or 2-(3-Methoxyphenyl)-2-(ethylamino)-cyclohexanone (Figure 1), commonly referred to as "MXE" or "3-MeO-2-Oxo-PCE," is a new compound for sale over the Internet. Methoxetamine was originally publicized through an interview with an "underground chemist" who envisioned its dissociative properties and proposed that it would be "a stress-free version of ketamine" [1]. Although not currently scheduled under the U.S. Controlled Substances Act,

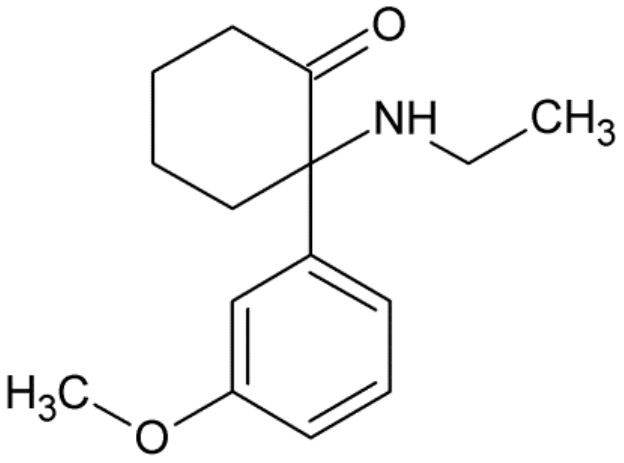


Figure 1 - Structure of methoxetamine.

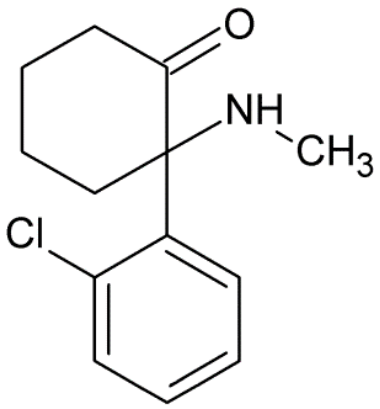


Figure 2 - Structure of ketamine.

methoxetamine may be considered to be an analog of ketamine (Figure 2) [2]; replacing the *ortho* chlorine in ketamine with a *meta* methoxy, and replacing the N-methyl with an N-ethyl. Herein, we report the structural elucidation of methoxetamine through nuclear magnetic resonance spectroscopy, mass spectrometry, infrared spectroscopy, and subsequent independent synthesis. The analytical data are also compared to the structurally similar drug ketamine. Additionally, analytical profiles of methoxetamine's synthetic intermediates and its major synthetic impurity are presented to assist forensic chemists who may encounter these substances in casework.

Experimental

Chemicals, Reagents, and Materials

All solvents were distilled-in-glass products of Burdick and Jackson Labs (Muskegon, MI). All other chemicals and NMR solvents were of reagent-grade quality and products of Aldrich Chemical (Milwaukee, WI). Ketamine HCl was obtained from the reference materials collection maintained at this laboratory.

Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were obtained on an Agilent VNMRS 600 MHz NMR using a 5 mm Protune broad band detection, variable temperature, pulse field gradient probe (Agilent, Palo Alto, CA). The HCl salts of the samples were initially dissolved in

deuterochloroform ($CDCl_3$) containing 0.03% v/v tetramethylsilane (TMS) as the 0 ppm reference compound, and later base extracted using saturated sodium bicarbonate in D_2O. The sample temperature was maintained at 26°C. Standard Agilent pulse sequences were used to collect the following spectra: proton, carbon (proton decoupled), and gradient versions of the 2-dimensional experiments COSY, HSQC, and HMBC. Data processing and structure elucidation were performed using Structure Elucidator software from Applied Chemistry Development (ACD/Labs, Toronto, Canada).

Gas Chromatography/Mass Spectrometry (GC/MS)

Mass spectra were obtained on an Agilent Model 5975C quadrupole mass-selective detector (MSD) that was interfaced with an Agilent Model 7890A gas chromatograph. The MSD was operated in the electron ionization (EI) mode with an ionization potential of 70 eV, a scan range of 34-600 amu, and a scan rate of 2.59 scans/s. The GC was fitted with a 30 m x 0.25 mm ID fused-silica capillary column coated with 0.25 µm 100% dimethylpolysiloxane, DB-1 (J & W Scientific, Rancho Cordova, CA). The oven temperature was programmed as follows: Initial temperature, 100°C; initial hold, 0.0 min; program rate, 6°C/min; final temperature, 300°C; final hold, 5.67 min. The injector was operated in the split mode (21.5:1) at 280°C. The MSD source was operated at 230°C.

Infrared Spectroscopy (FTIR)

Infrared spectra were obtained on a Thermo-Nicolet Nexus 670 FTIR equipped with a single bounce attenuated total reflectance (ATR) accessory. Instrument parameters were: Resolution = 4 cm^{-1}; gain = 8; optical velocity = 0.4747; aperture = 150; and scans/sample = 16.

Synthesis of Methoxetamine

In accordance with Journal policy, exact experimental details are not provided. A procedure analogous to that of ketamine was utilized (Figure 3) for the preparation of methoxetamine and its intermediates [3].

Results and Discussion

NMR Elucidation

Proton and carbon NMR spectra as well as the assignments for methoxetamine HCl and ketamine HCl are presented in Figures 4-7. Assignments were based on proton chemical shifts and peak patterns, carbon chemical shifts, HSQC (1 bond carbon to proton correlations), HMBC (2-4 bond carbon to proton correlations), and COSY (2-3 bond proton-proton correlations) spectra. Assignments were further confirmed using ACD Structure Elucidator software.

The methoxetamine spectra (carbon and HSQC) contain 15 carbons: 1 ketone, 6 benzene (4 protonated), 1 aliphatic quaternary, 5 methylenes, and 2 methyls. The aromatic proton peak pattern for methoxetamine base clearly shows a 1,3-disubstituted benzene pattern: a triplet (7.29 ppm), a doublet (6.82 ppm), a doublet of doublets (6.82 ppm), and 1 small coupling doublet (6.79 ppm). In addition, the proton, carbon, and COSY spectra indicate the presence of an $N\text{-}CH_2\text{-}CH_3$ whose methylene protons are not equivalent, the presence of a methoxy singlet at 3.8-3.9 ppm, and 4 methylenes bonded to each other in an *n*-butyl chain (as indicated by the multiple couplings to each proton and the COSY correlations). HMBC correlations show that the butyl chain is bonded to or very nearby the ketone carbon and the quaternary aliphatic carbon. The HMBC also indicates that the N-ethyl group, the *n*-butyl group and the benzene ring are bonded to or very nearby the quaternary carbon. Based on the molecular weight of 247 and the NMR data, the molecular formula is $C_{15}H_{21}NO_2$. This formula indicates that there are 6 unsaturations and/or rings in the molecule: the benzene ring accounts for 4 and the ketone for 1, thus leaving 1 additional ring (no other unsaturations noted in spectra). The main NMR fragments are a benzene ring (with a methoxy at C3), a ketone, an N-ethyl, a quaternary carbon, and an *n*-butyl chain. The quaternary carbon chemical shift (69.7 ppm base) indicates it is bonded to one or more strong electron withdrawing groups. The structure of methoxetamine satisfies all this and also gives the lowest derivations of carbon chemical shifts (i.e., experimental versus calculated).

In contrast to methoxetamine, the ketamine base proton spectrum (Figure 7) displays two "doublet of doublets" (7.38 and 7.55 ppm) and two "triplet of doublets" (7.25 and 7.32 ppm) in the aromatic region, and a singlet at 2.10 ppm for the N-methyl group. The proton and carbon spectra of ketamine and methoxetamine are very different and are easily distinguished.

Mass Spectral Elucidation

The mass spectra of methoxetamine and ketamine are shown in Figure 8. The appearance of the mass spectrum of methoxetamine is similar to that of ketamine, at least at the higher mass range. The major dissimilarities between the two spectra are a difference of +10 Daltons for the peaks of methoxetamine versus the corresponding peaks of ketamine (base peak of *m/z* 190 versus *m/z* 180; peak at *m/z* 204 versus *m/z* 194; and peak at *m/z* 219 versus *m/z* 209).

The proposed fragmentation of methoxetamine is shown in Figure 9. Due to the similarity of the structures, the major fragmentation mechanisms of methoxetamine are expected to be similar to that proposed for ketamine [4]. Initial ionization occurs at the amine nitrogen which is followed by *alpha* cleavage to give structure A. Structure A can undergo neutral loss of CO to yield ion B, *m/z* 219. The newly formed radical site in structure B can undergo secondary *alpha* cleavages. Loss of a hydrogen radical from structure B (pathway a) results in structure C, *m/z* 218. Loss of neutral ethylene from structure B (pathway b) gives structure D, *m/z* 191 which likewise can lose a hydrogen radical to give structure E, *m/z* 190.

Structure B can also undergo ring closure (pathway c) to yield a radical cation (structure F) similar in stability to the parent ion. This ion can undergo further *alpha* cleavages to yield ions G, *m/z* 204 (loss of a methyl radical) and H, *m/z* 112 (loss of a methoxyphenyl radical).

FTIR

The FTIR spectra for methoxetamine HCl and ketamine HCl are illustrated in Figure 10. Comparison reveals somewhat similar absorption patterns, with the most prominent differences being in the region of 500-1600 cm^{-1}. An absorbance found at 1725 cm^{-1} (due to a carbonyl stretching vibration) strongly indicates a carbonyl in the suspected methoxetamine (carbonyl

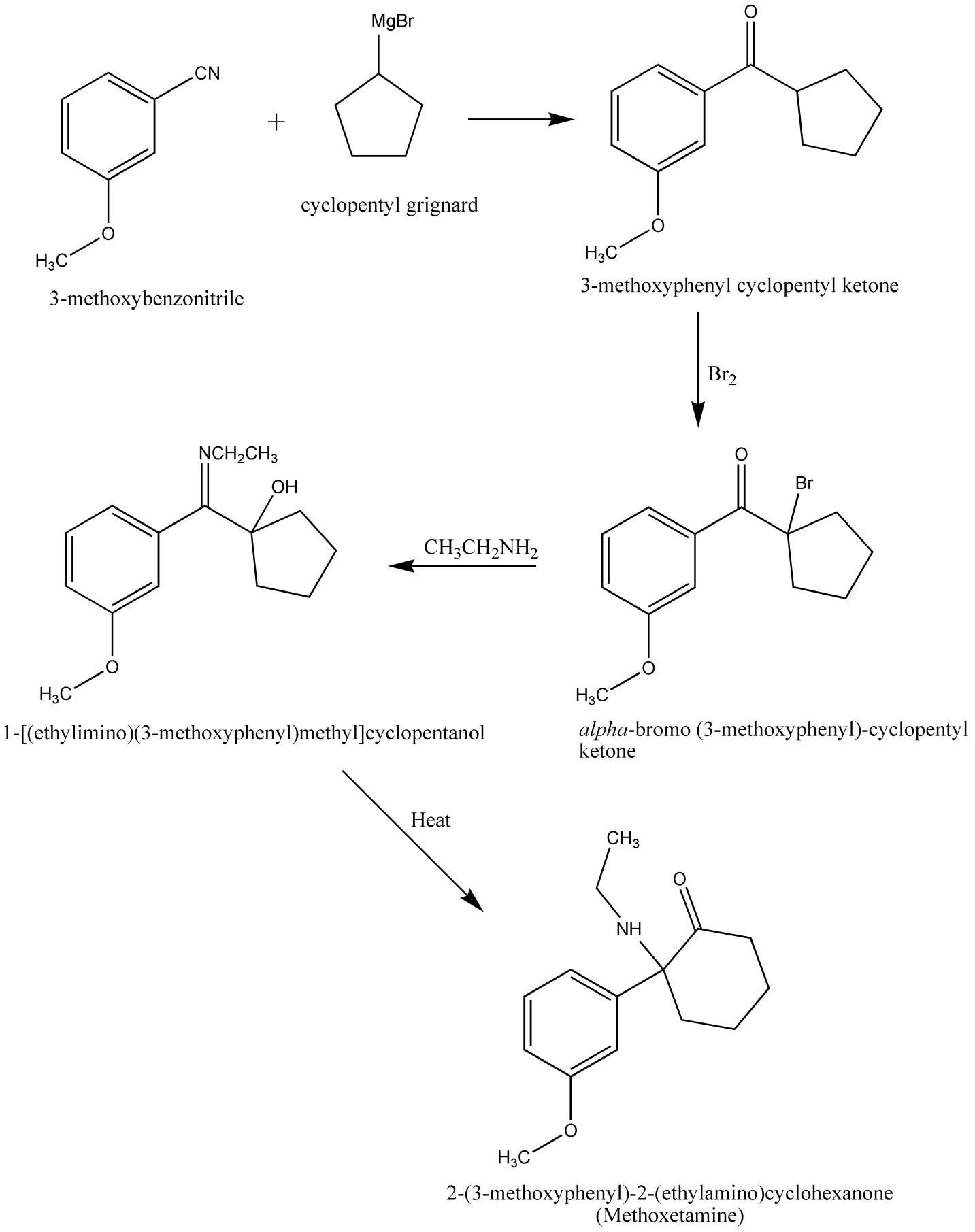
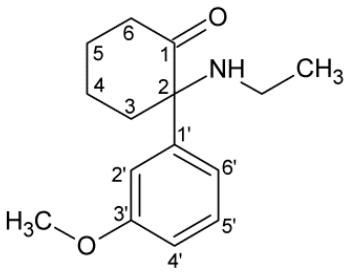


Figure 3 - Synthetic route for methoxetamine.

Position	Carbon (ppm)	Proton (ppm, J)	Structure
1	205.1	-	
2	73.2	-	
3	35.7	2.74 td(13.9, 3.8) , 3.42 dq(13.9, 2.7 Hz)	
4	21.7	1.62 qt(13.3,3.3 Hz), 1.85 m	
5	27.5	1.89 m, 1.98 m	
6	40.0	2.60 m	
N-**CH$_2$**-CH$_3$	39.9	2.44 m, 3.03 m	
N-CH$_2$-**CH$_3$**	12.2	1.42 t(7.3 Hz)	
1'	132.9	-	
2'	116.5	~6.97 bs	
3'	160.7	-	
4'	113.7	7.26 bs	
5'	130.5	7.37 t(8.0 Hz)	
6'	121.2	6.97 dd(8.0, 2.6 Hz)	
OCH$_3$	55.8	3.89 s	
NH$_2$	-	9.55 bs, 10.18 bs	
		b = broad, d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet	



HCl

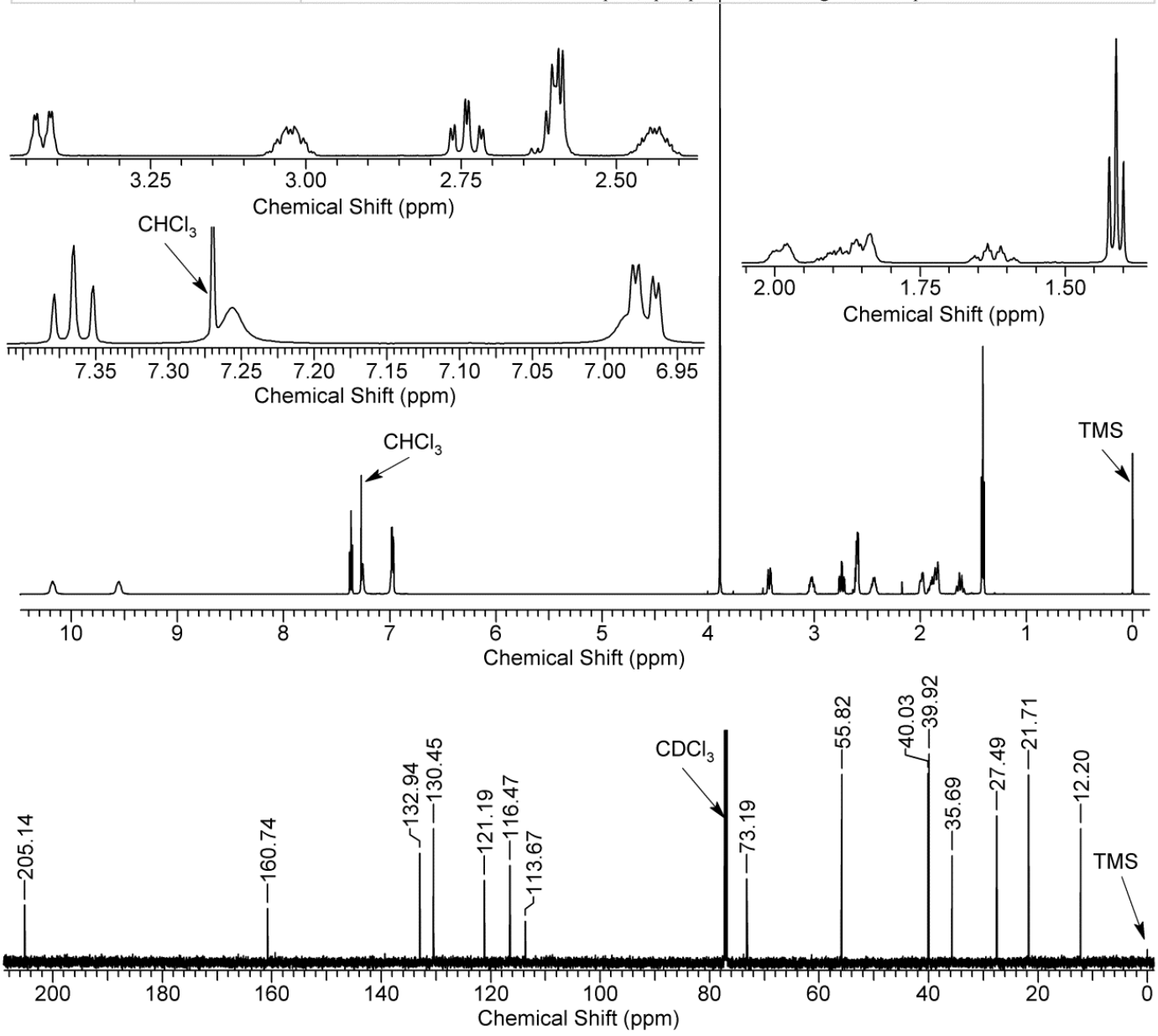
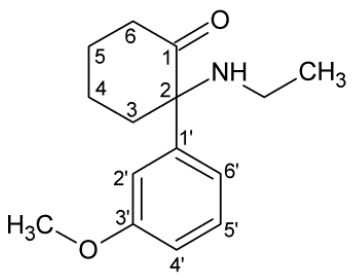


Figure 4 - ^{1}H and ^{13}C NMR data for methoxetamine HCl.

Position	Carbon (ppm)	Proton (ppm, J)	Structure
1	211.2	-	
2	69.7	-	
3	36.1	1.83 m, 2.86 m	
4	22.4	1.76 m, 1.83 m	
5	27.6	1.71 m, 1.95 m	
6	39.8	2.33 m, 2.40 m	
N-**CH_2**-CH_3	36.6	2.06 dq(10.6, 6.9 Hz), 2.29 m	
N-CH_2-**CH_3**	15.7	0.99 t(6.9 Hz)	
1'	141.1	-	
2'	113.2	6.79 d(2.5 Hz)	
3'	160.0	-	
4'	112.3	6.82 dd(8.1, 2.5 Hz)	
5'	129.8	7.29 t(8.1 Hz)	
6'	119.4	6.82 d(8.1 Hz)	
OCH_3	55.3	3.8 s	
		d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet	



base

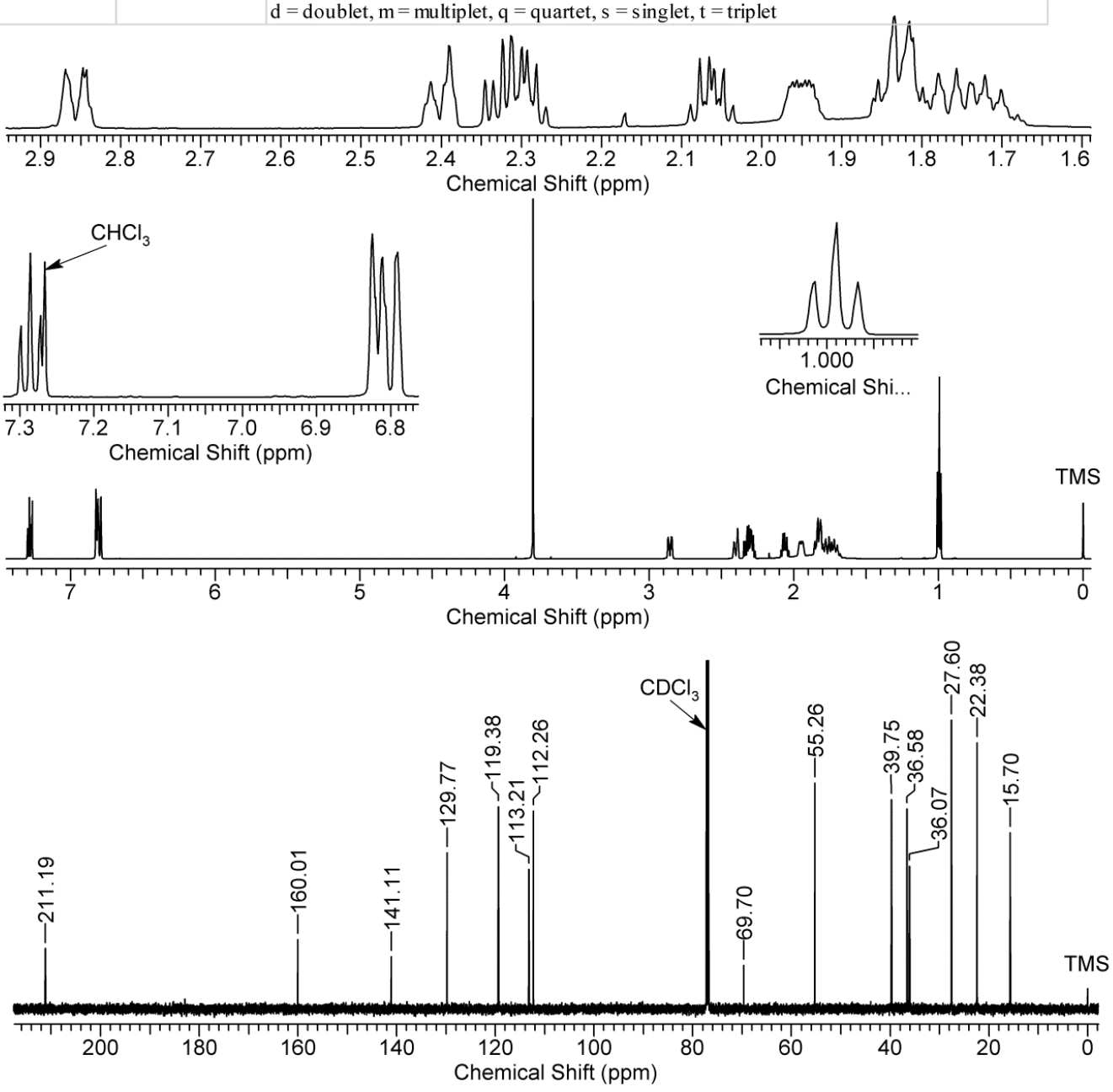
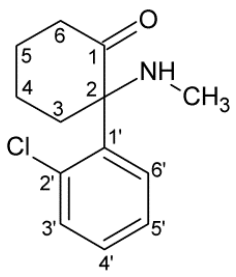


Figure 5 - ^{1}H and ^{13}C NMR data for methoxetamine base.

Position	Carbon (ppm)	Proton (ppm, J)	Structure
1	205.9	-	
2	72.7	-	
3	38.8	2.28 td (14.2, 3.8 Hz), 3.52 dm(14.2 Hz)	
4	21.7	1.58 m, 1.86 m	
5	29.7	1.85 m, 2.06 m	
6	40.4	2.59 td(12.8, 6.0 Hz), 2.69 dm(12.8 Hz)	
1'	135.3	-	
2'	128.8	-	
3'	131.8	7.49 m	
4'	132.1	7.47 m	
5'	128.5	7.56 ddd(8.3, 6.5, 2.0 Hz)	
6'	132.0	8.02 d(8.3 Hz)	
NCH_3	28.3	2.53 s	

d = doublet, m = multiplet, s = singlet, t = triplet

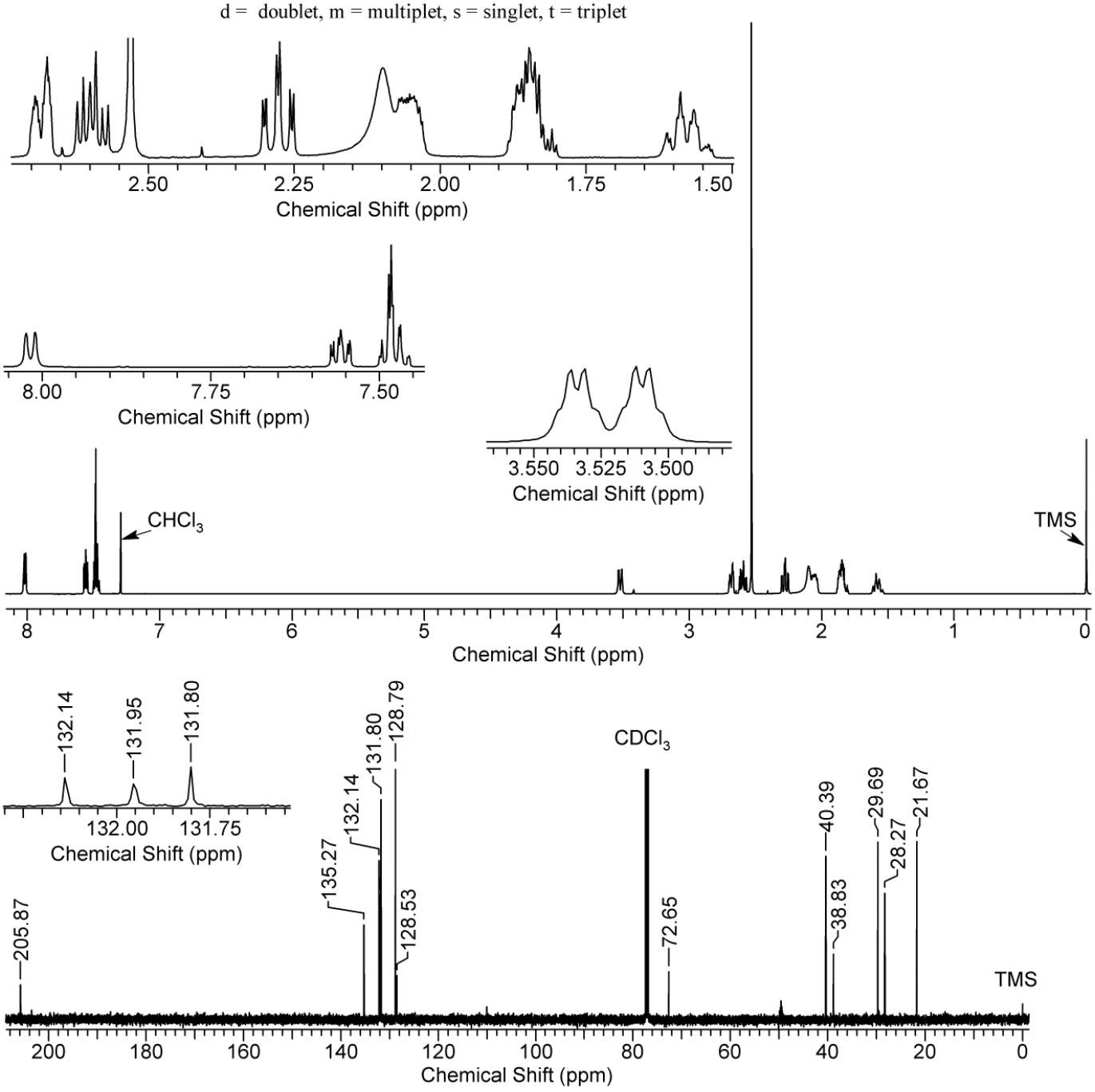
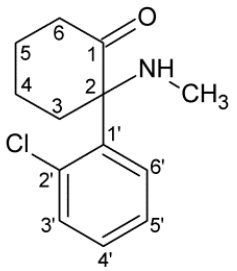


Figure 6 - ^{1}H and ^{13}C NMR data for ketamine HCl.

Position	Carbon (ppm)	Proton (ppm, J)	Structure
1	209.2	-	
2	70.2	-	
3	38.7	1.77 m, 2.78 m	
4	21.9	1.77 m	
5	28.1	1.87 m, 2.00 m	
6	39.6	2.46 ddd(13.5, 8.6, 5.0 Hz), 2.51 ddd(13.5, 7.2, 5.3 Hz)	
1'	137.8	-	
2'	133.8	-	
3'	131.3	7.38 dd(7.6, 1.4 Hz)	
4'	128.7	7.25 td(7.6, 1.8 Hz)	
5'	126.6	7.32 td(7.6, 1.4 Hz)	
6'	129.4	7.55 dd(7.6, 1.8 Hz)	
NCH_3	29.1	2.10 s	



base

d = doublet, m = multiplet, s = singlet, t = triplet

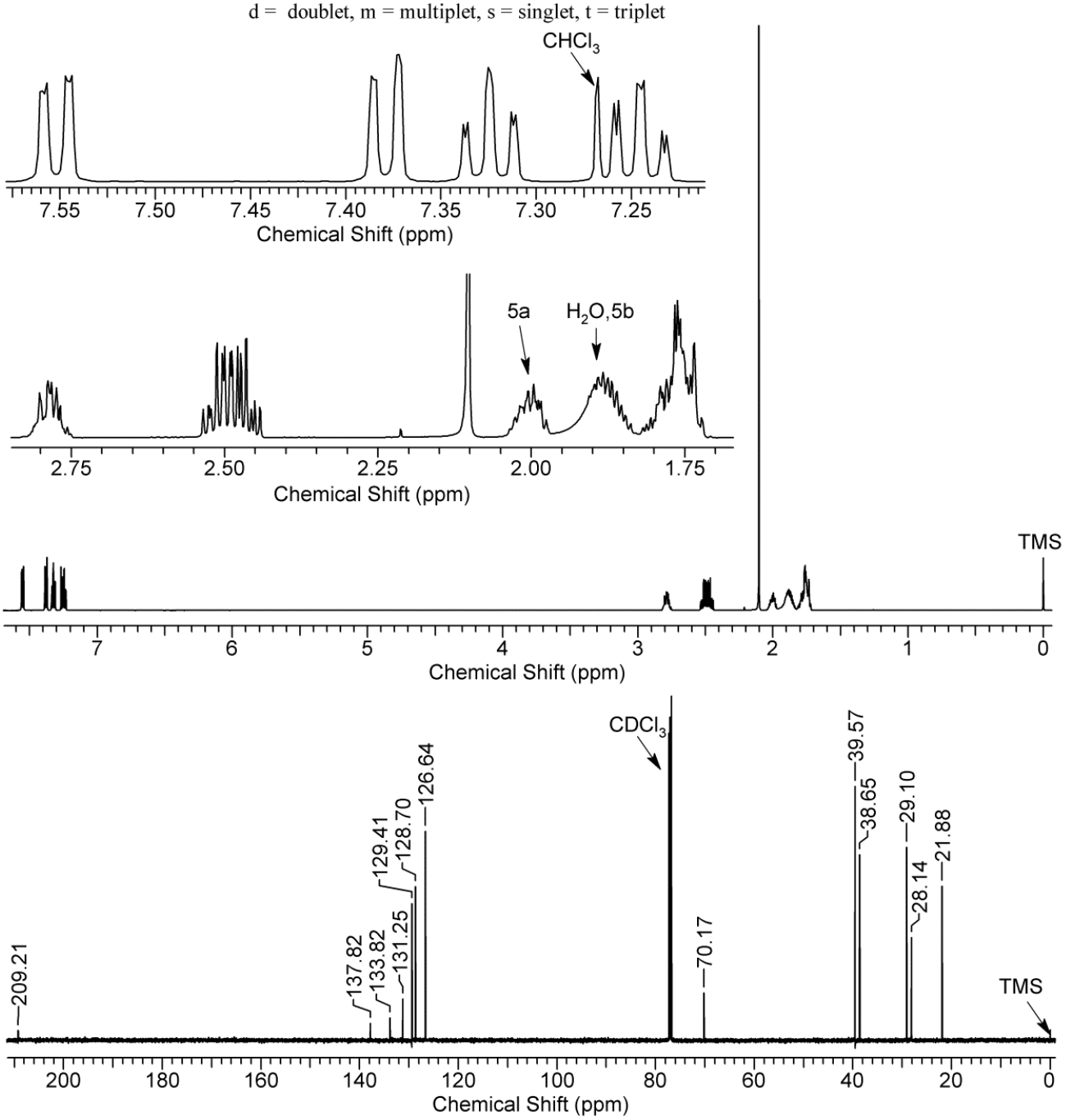


Figure 7 - ^{1}H and ^{13}C NMR data for ketamine base.

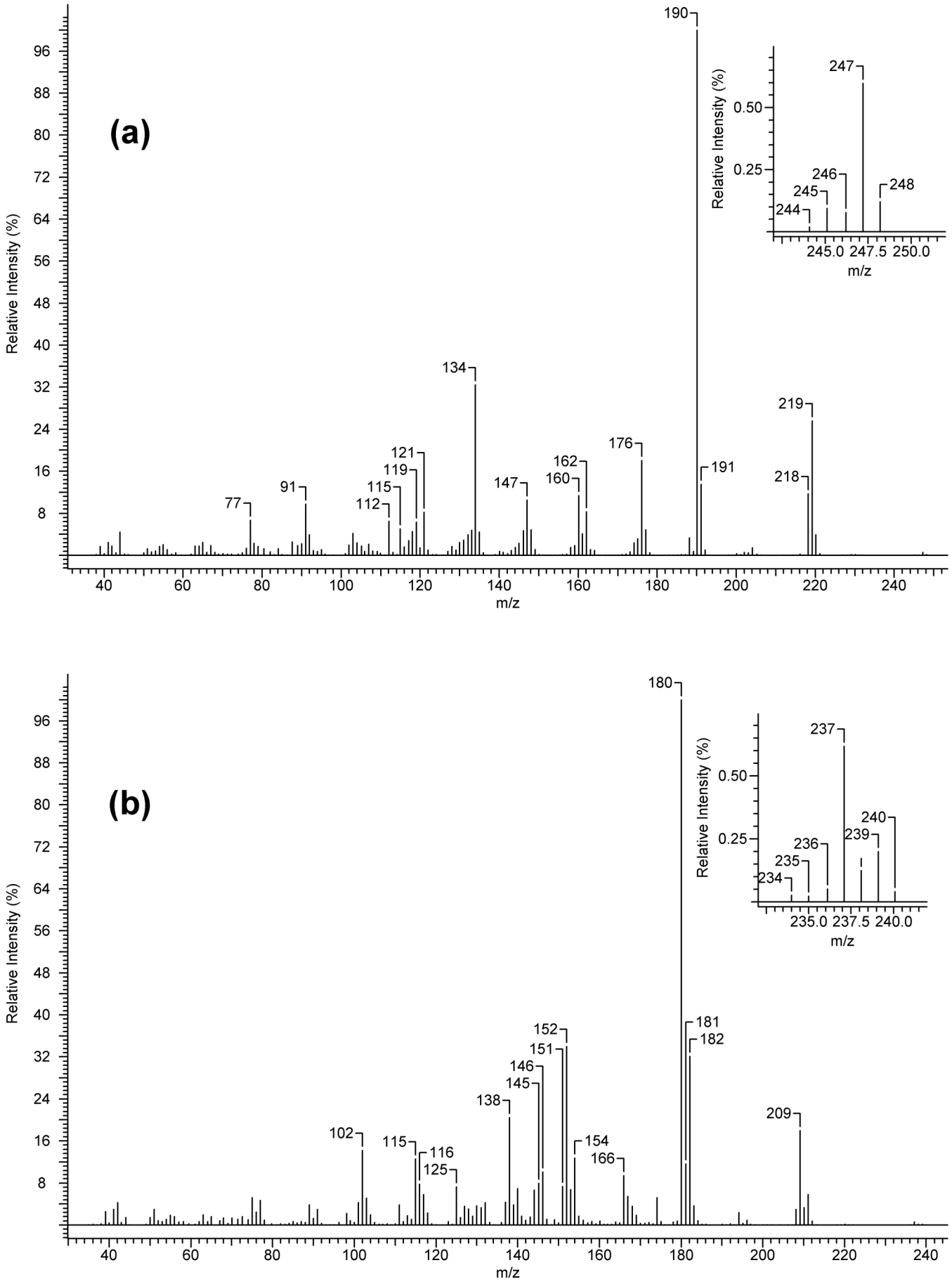


Figure 8 - Mass spectra of (a) methoxetamine HCl and (b) ketamine HCl.

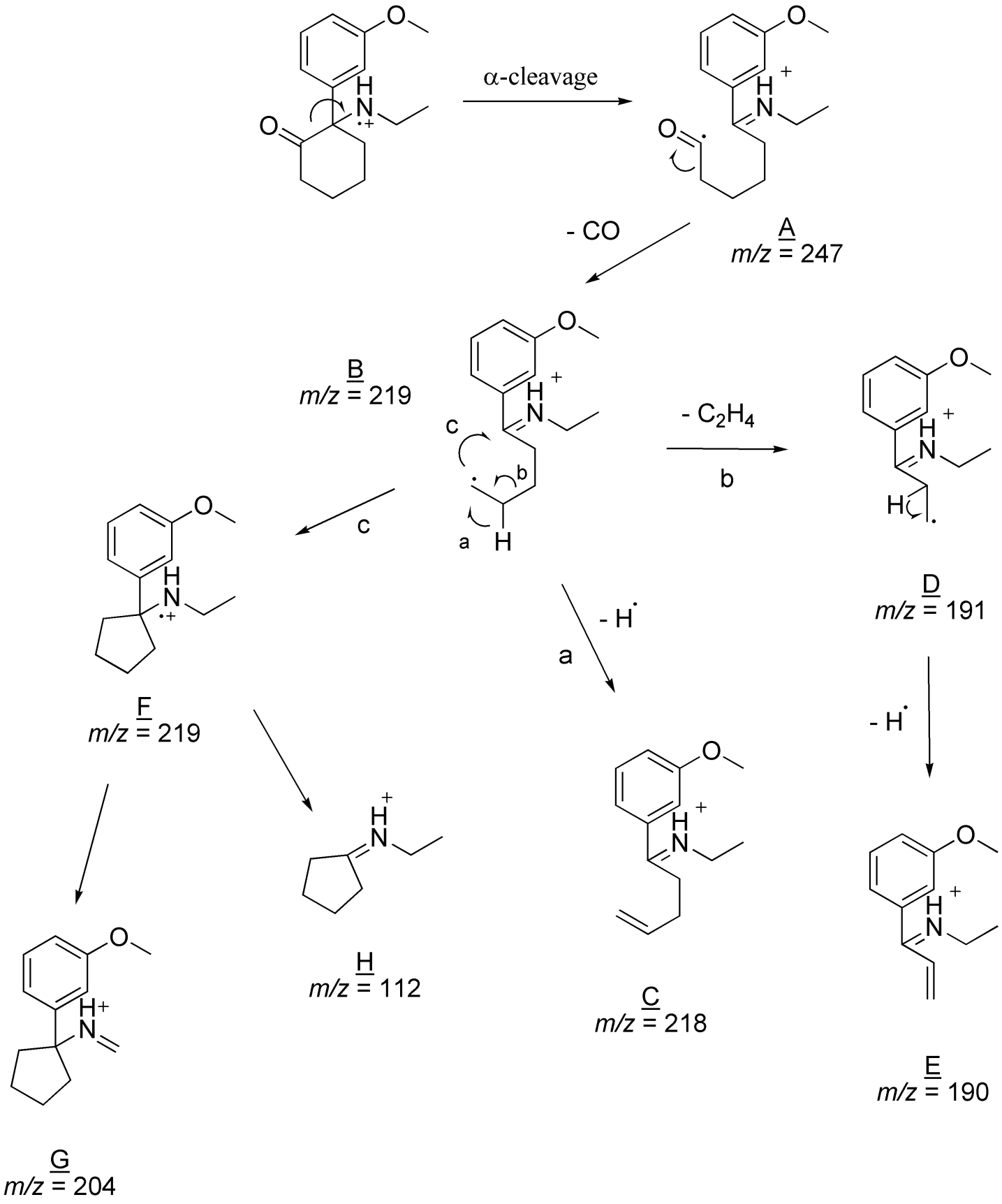


Figure 9 - Proposed fragmentation pathways for methoxetamine.

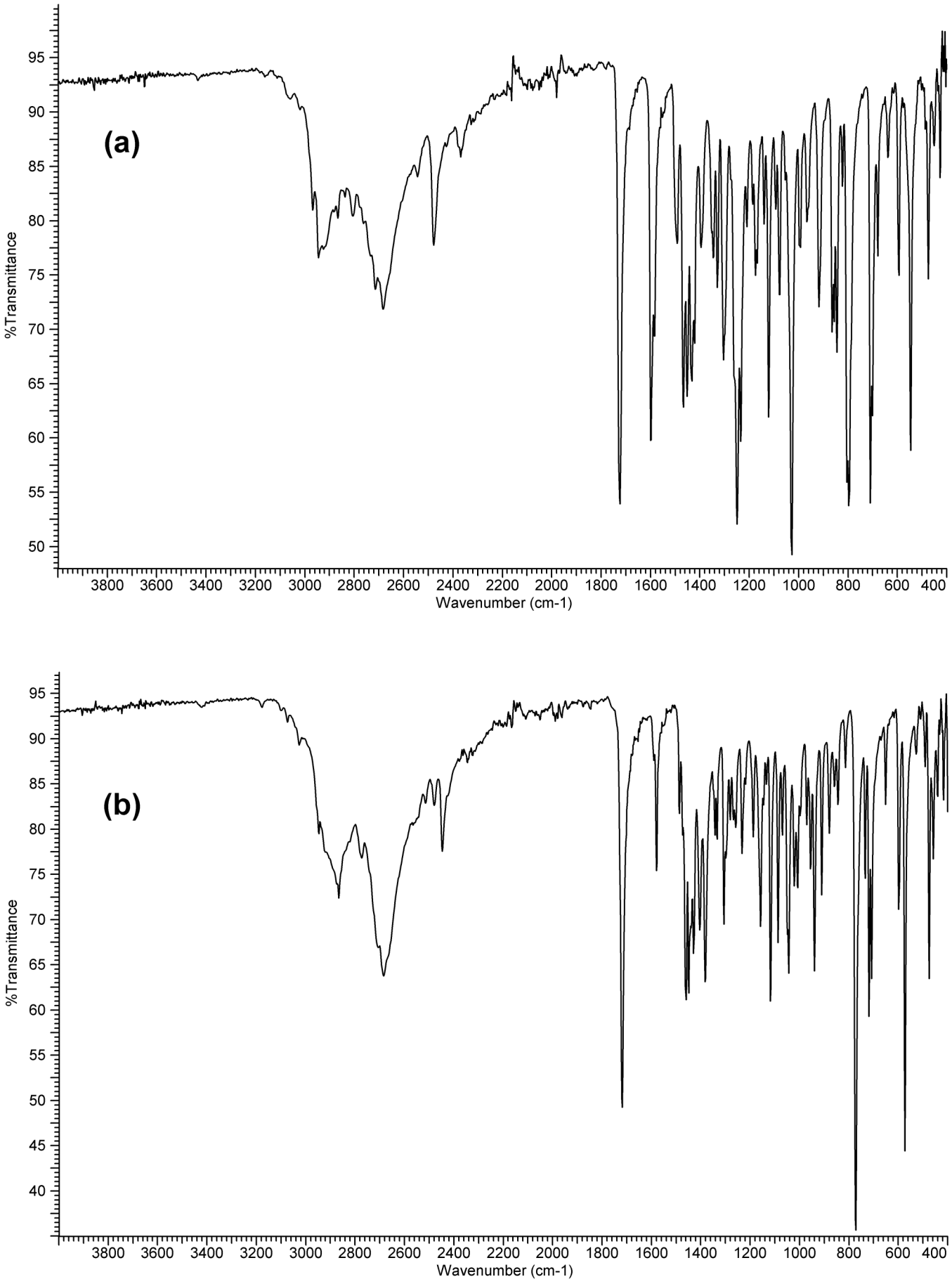


Figure 10 - FTIR spectra of (a) methoxetamine HCl and (b) ketamine HCl.

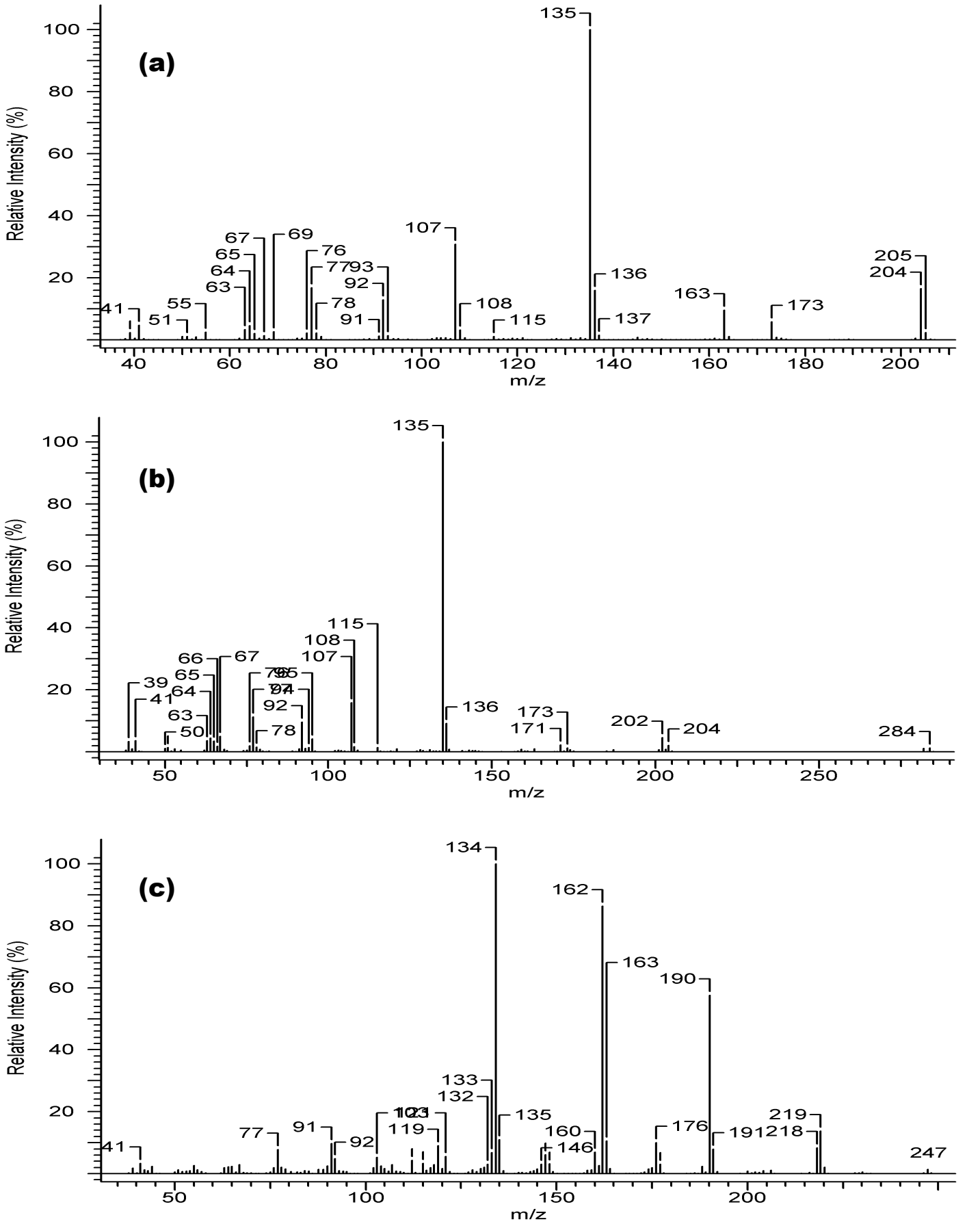


Figure 11 - Mass spectra of (a) 3-methoxyphenyl cyclopentyl ketone, (b) *alpha*-bromo-(3-methoxyphenyl)-cyclopentyl ketone, and (c) 1-[(ethylimino)(3-methoxyphenyl)methyl]cyclopentanol.

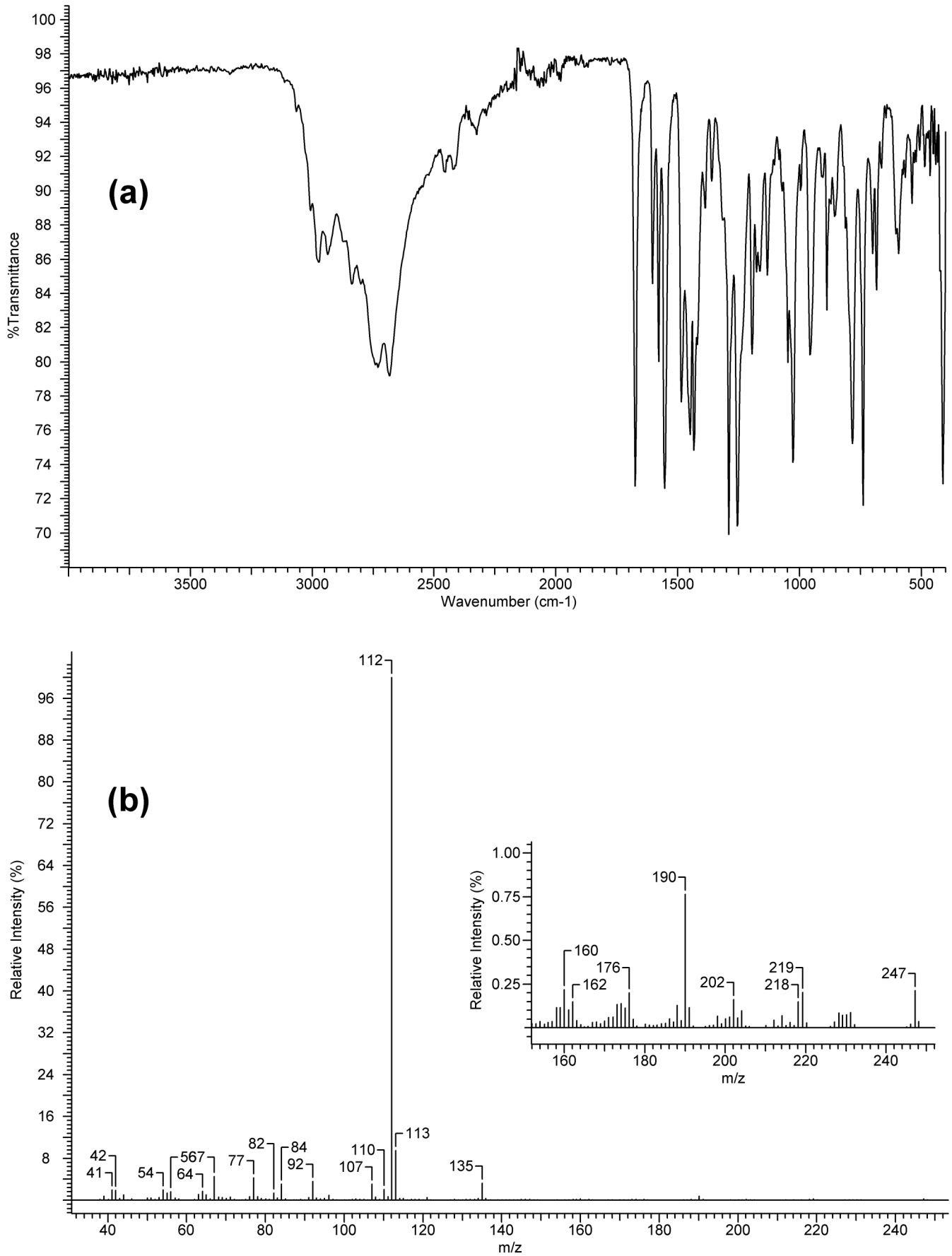
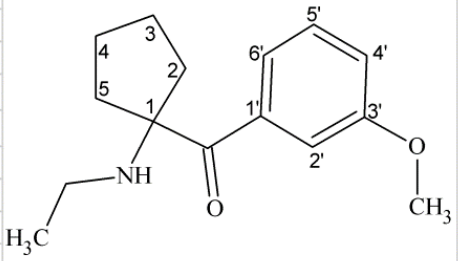


Figure 12 - Infrared spectrum (a) and mass spectrum (b) of [1-(ethylamino)cyclopentyl](3-methoxyphenyl)methanone; methoxetamine synthesis impurity.

Position	Carbon (ppm)	Proton (ppm, J)	Structure
1	77.2	-	
2	35.5	2.57 dt(13.6, 6.9 Hz), 2.67 dt (13.6, 7.0 Hz)	
3	26.0	1.84 m, 2.29 m	
4	26.0	1.84 m, 2.29 m	
5	35.5	2.57 dt(13.6, 6.9 Hz), 2.67 dt (13.6, 7.0 Hz)	
C=O	196.8	-	
N-**CH$_2$**-CH$_3$	41.0	2.91 m	
N-CH$_2$-**CH$_3$**	12.2	1.50 t(7.2 Hz)	
1'	134.7	-	
2'	113.4	7.43 dd(2.3, 2.0 Hz)	
3'	160.1	-	
4'	120.2	7.15 dd(8.4, 2.3 Hz)	
5'	130.2	7.47 dd(8.4, 7.6 Hz)	
6'	121.3	7.81 dd(7.6, 2.0 Hz)	
OCH$_3$	55.6	3.87 s	
NH2	-	9.99 bs	
		b = broad, d = doublet, m = multiplet, s = singlet, t = triplet	



HCl

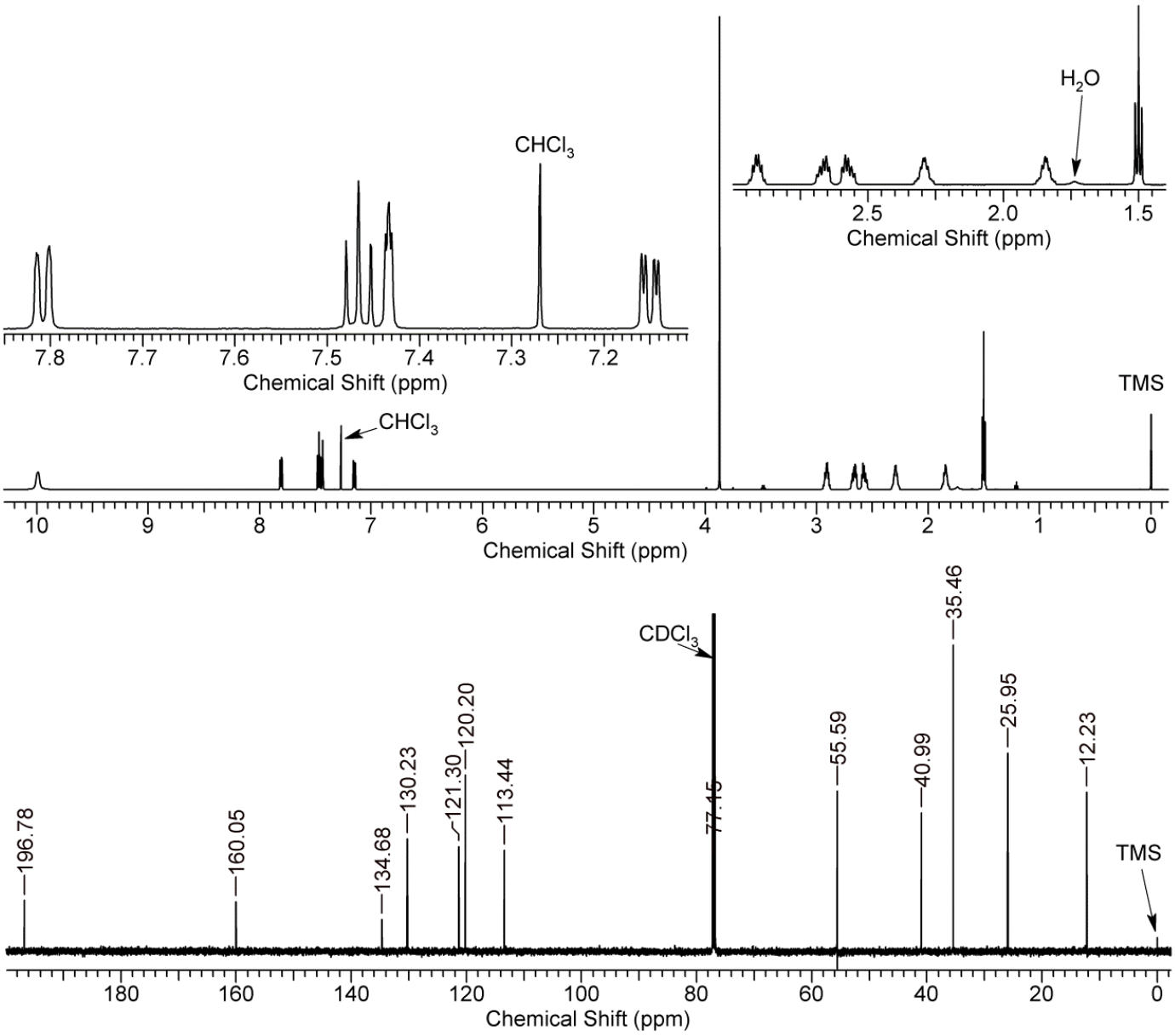
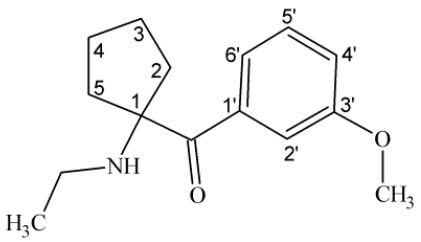


Figure 13 - ^{1}H and ^{13}C NMR data for [1-(ethylamino)cyclopentyl](3-methoxyphenyl)methanone HCl.

Position	Carbon (ppm)	Proton (ppm, J)	Structure
1	75.2	-	
2	36.7	1.78 m, 2.31 m	
3	24.7	1.66 m, 1.78 m	
4	24.7	1.66 m, 1.78 m	
5	36.7	1.78 m, 2.31 m	
C=O	204.5	-	
N-**CH2**-CH3	39.1	2.40 q(7.2 Hz)	
N-CH2-**CH3**	15.9	0.93 t(7.2 Hz)	
1'	137.9	-	
2'	114.0	7.72 dd(2.2, 1.9 Hz)	
3'	159.4	-	
4'	118.1	7.05 dd(8.0, 2.2 Hz)	
5'	129.0	7.32 t(8.0 Hz)	
6'	121.4	7.76 dd(8.0, 1.9 Hz)	
OCH3	55.4	3.85 s	
		d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet	



base

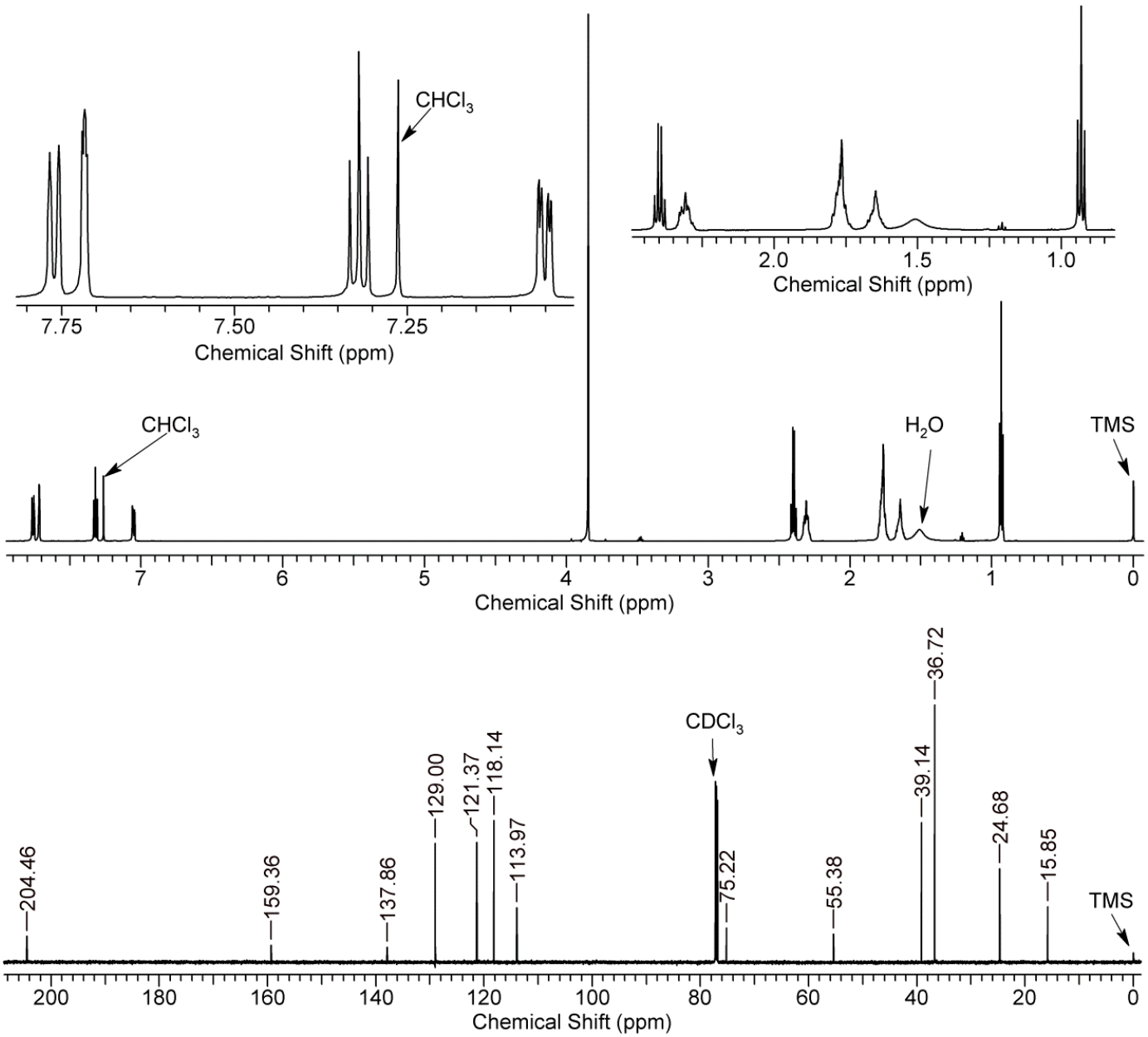


Figure 14 - ^{1}H and ^{13}C NMR data for [1-(ethylamino)cyclopentyl](3-methoxyphenyl)methanone base.

Table 1 - Gas chromatographic retention times (R_t) for the methoxetamine and related compounds[a].

Compound	R_t (min)
3-methoxyphenyl cyclopentyl ketone	14.50
1-hydroxycyclopentyl-(3-methoxyphenyl)-ketone-N-ethylimine	16.31
ketamine	16.51
methoxetamine	17.21
[1-(ethylamino)cyclopentyl](3-methoxyphenyl)methanone	17.35
alpha-bromo-(3-methoxyphenyl)-cyclopentyl ketone	17.54

[a]Conditions given in the experimental section.

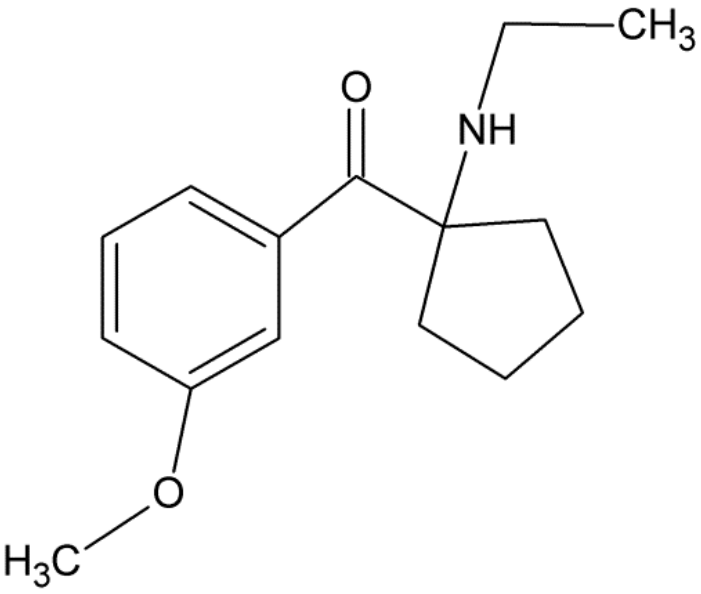


Figure 15 - Structure of methoxetamine impurity.

stretch for ketamine is found at 1719 cm^{-1}). When methoxetamine HCl is compared to ketamine HCl, significant differences can differentiate the compounds, especially the absorbances at 1550-1600 cm^{-1} due to C-C stretching [5].

Synthesis

Methoxetamine was synthesized utilizing an analogous procedure for that of ketamine (Figure 3). A cyclopentyl Grignard was reacted with 3-methoxybenzonitrile to form 3-methoxyphenyl cyclopentyl ketone, which was then brominated *alpha* to the ketone. The *alpha*-bromo ketone was converted to the Schiff's base with ethyl amine, which was then heated to form methoxetamine. The NMR, FTIR, and mass spectrum of the synthesized methoxetamine were in all respects identical to the unknown compound's spectra. Mass spectra for the three intermediates are illustrated in Figure 11. GC retention time data for the respective compounds are presented in Table 1.

A significant amount of a by-product (impurity) was produced during the synthesis of methoxetamine. The FTIR (Figure 12a) of the synthesis impurity indicated that a carbonyl was present and its mass spectrum (Figure 12b) indicated a molecular weight of 247. The impurity was easily isolated from methoxetamine HCl by its solubility in acetone. The NMR spectrum (Figures 13 and 14) illustrated that this compound, like methoxetamine, contained a 1,3-disubstituted benzene (with a methoxy group at C3), an N-ethyl group, a ketone, a quaternary carbon, and an *n*-butyl chain. However, the proton and carbon chemical shifts and the HMBC correlations show that the ketone is the bridge between the benzene ring and a cyclopentyl ring and this cyclopentyl ring contains the quaternary carbon which is bonded to the N-ethyl group. The isolated impurity was characterized as [1-(ethylamino)cyclopentyl](3-methoxyphenyl)methanone (Figure 15).

References

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