The Characterization of α-Pyrrolidinopentiophenone

John F. Casale* and Patrick A. Hays
U.S. Department of Justice
Drug Enforcement Administration
Special Testing and Research Laboratory
22624 Dulles Summit Court
Dulles, VA 20166-9509
[email address withheld at authors' request]

ABSTRACT: The synthesis, analysis, and characterization of α-pyrrolidinopentiophenone (commonly referred to as "*alpha*-PVP," "α-PVP," or "O-2387") are briefly discussed. Analytical data (mass spectrometry, nuclear magnetic resonance spectroscopy, and infrared spectroscopy) are presented.

KEYWORDS: α-pyrrolidinopentiophenone, *alpha*-PVP, 1-phenyl-2-(1-pyrrolidinyl)-1-pentanone, designer drug, synthesis, characterization, forensic chemistry.

This laboratory recently received a request to synthesize α-pyrrolidinopentiophenone; 1-phenyl-2-(1-pyrrolidinyl)-1-pentanone (Figure 1) as a primary standard for identification of this compound in a number of drug exhibits. Although there are two literature citations for this compound [1,2], insufficient analytical data is available for forensic identification. α-Pyrrolidinopentiophenone is not currently scheduled under the U.S. Controlled Substances Act; however, it may be considered a controlled substance analogue of 3,4-methylene-dioxypyrovalerone (MDPV, placed in Schedule I on October 21, 2011) [3]. Herein, we report its synthesis and analytical profile (nuclear magnetic resonance, mass spectrometry, and infrared spectroscopy), to assist forensic chemists who may encounter this substance 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).

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.

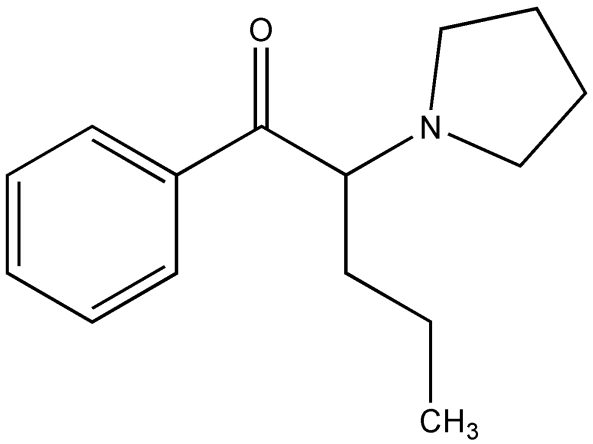


Figure 1 - Structural formula of α-pyrrolidinopentiophenone.

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.

Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were obtained on an Agilent 400MR NMR with a 400 MHz magnet, a 5 mm Protune indirect detection, variable temperature, pulse field gradient probe (Agilent, Palo Alto, CA). 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 HSQC, and HMBC. Data processing and structure elucidation were performed using Structure Elucidator software from Applied Chemistry Development (ACD/Labs, Toronto, Canada).

Synthesis of α-Pyrrolidinopentiophenone

In accordance with Journal policy, exact experimental details are not provided, but are outlined in Figure 2. Briefly, 1-phenyl-1-pentanone was formed from the reaction of valeronitrile with phenylmagnesium bromide, with subsequent acidic workup. The pentanone was then brominated to form the *alpha*-bromo ketone, which was then reacted with pyrrolidine to give the title compound, which was finally converted to the HCl ion pair.

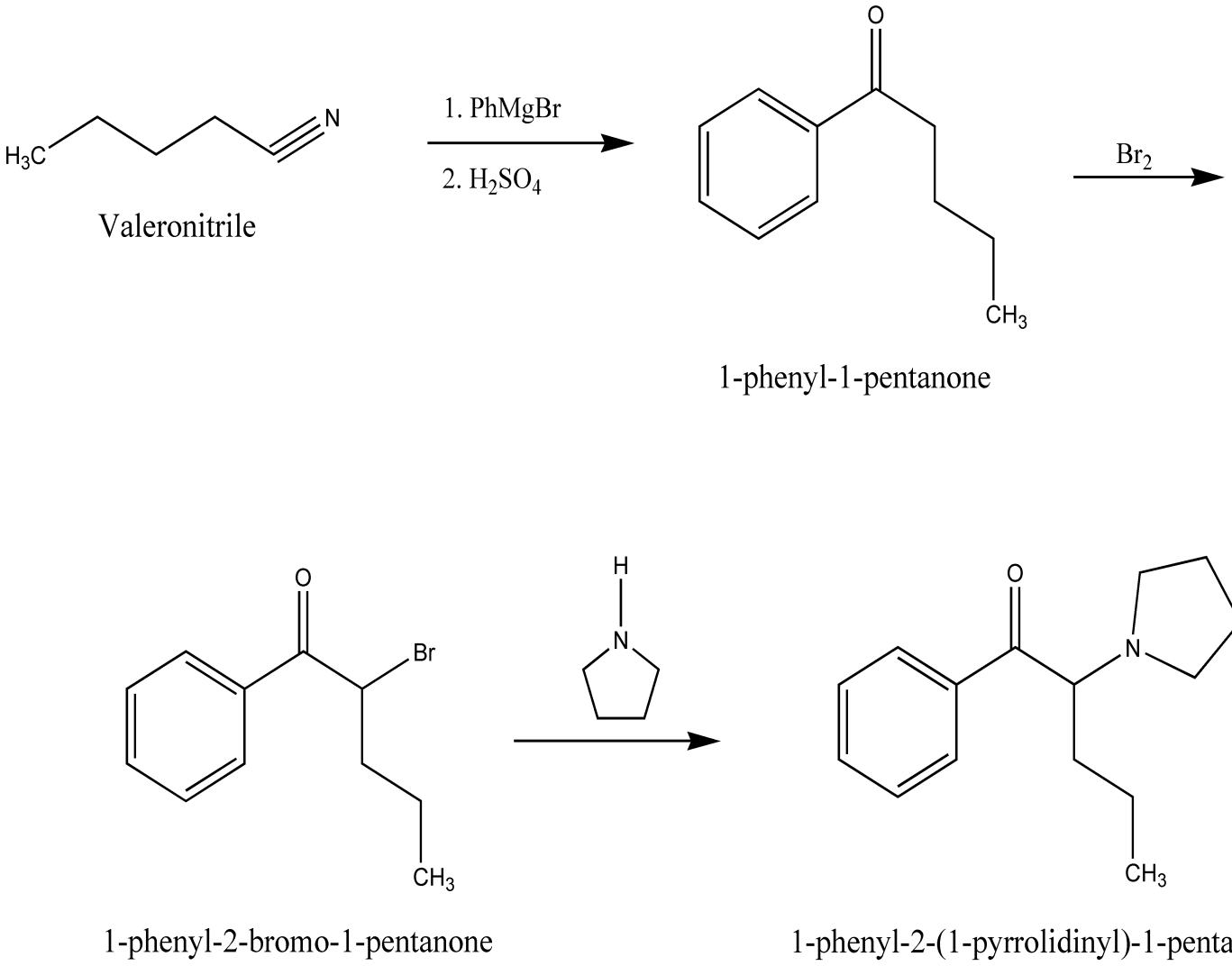


Figure 2 - Synthetic route for *α*-pyrrolidinopentiophenone.

Results and Discussion

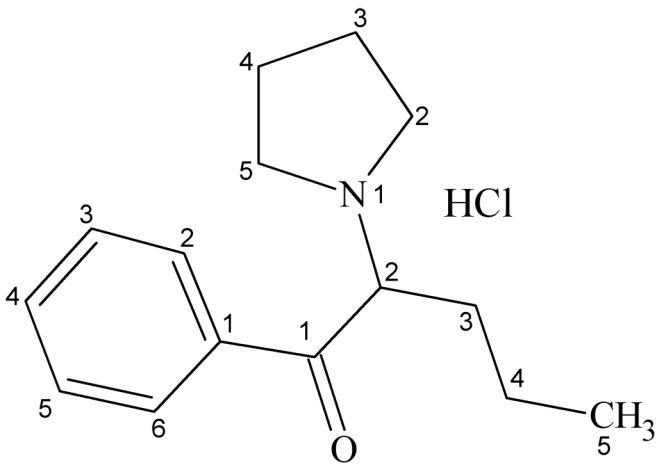
Structural Elucidation/Confirmation of α-Pyrrolidinopentiophenone HCl

NMR experiments (proton, carbon, COSY, NOESY, HSQC, and HMBC) were performed on the HCl ion pair dissolved in $CDCl_3$ (containing TMS as the 0 ppm reference), giving the proton spectrum and assignments found in Figure 3. The solution was base extracted with sodium bicarbonate saturated D_2O, and the $CDCl_3$ layer was isolated and dried with anhydrous sodium sulfate. The proton spectrum and assignments for the free base are found in Figure 4. The HCl ion pair proton spectrum shows a broad 1H singlet at 12.48 ppm indicating NH, a typical phenyl pattern at 7.56 ppm (*meta*, appears as a 2H triplet), 7.70 (*para*, appears as a 1H triplet), and 7.99 ppm (*ortho*, appears as a 2H doublet), and 16 aliphatic protons from 0.9-5.3 ppm. The carbon spectrum has 13 peaks translating to 15 carbons (1 ketone at 196.7 ppm, 6 aromatic in a typical 4 peak phenyl pattern, and 8 aliphatic). The HMBC, COSY, proton chemical shifts and peak patterns, and the carbon chemical shifts show the presence of a phenyl group, a pyrrolidine ring (the 4 carbons are not magnetically equivalent), and a 1,2-disubstituted pentane chain with C-1 being the ketone (there are HMBC correlations to the phenyl protons) and C-2 as a methine (whose proton and carbon chemical shifts indicate bonding to nitrogen, 5.26 ppm ^{1}H, 62.7 ppm ^{13}C) confirming the structure as *α*-pyrrolidinopentiophenone.

The NMR data of the base shows 21 protons and 11 carbons peaks translating to 15 carbons (1 ketone, 4 aromatic peaks that are 6 carbons, 6 aliphatic peaks that are 8 carbons). As the base, the pyrrolidine carbons produce only 2 signals (2 pair of magnetically equivalent methylenes). Comparing the HCl and base proton spectra shows what a large influence the acid has on the proton chemical shifts that are near the nitrogen. Most notably, the proton chemical shift of the methine of the 1,2-di-substituted pentane chain moves from 5.26 (HCl) to 3.91 ppm (base), while the pyrrolidine protons move from 2.0-3.8 ppm (HCl) to 1.7-2.7 ppm (base). Processing the NMR data with ACD Structure Elucidator software confirmed the structures.

The infrared and mass spectra of *α*-pyrrolidinopentiophenone are illustrated in Figures 5 and 6, respectively. The FTIR (Figure 5) exhibits a strong carbonyl stretch at 1681 cm^{-1}, aliphatic CH stretching at 2866-2958 cm^{-1}, and amine HCl bands at 2400-2800 cm^{-1}. The mass spectrum displays a weak M-2 ion at *m/z* 229 and base peak at *m/z* 126. Other ions in the spectrum are generally less than 10% of the base peak's intensity.

position	carbon (ppm)	proton (ppm)		J_{HH} (Hz)
Phenyl 1	135.7	-		
2,6	128.6	7.99	m	
3,5	129.4	7.56	m	
4	135.1	7.70	m	
1-Pentanone				
1 (C=O)	196.7			
2 (CH)	62.7	5.26	dt	8.0, 5.1
3	33.0	2.04, 2.20	m, m	
4	19.6	1.36, 1.48	m, m	
5	14.0	0.91	t	7.3
Pyrrolidine 1	-	12.48	bs	
2	49.4	3.62, 3.82	m, m	
3	23.7	2.20	m	
4	24.0	2.04, 2.20	m, m	
5a	52.9	2.93	dq	10.5, 7.7
5b	52.9	3.82	m	
b = broad, d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet				



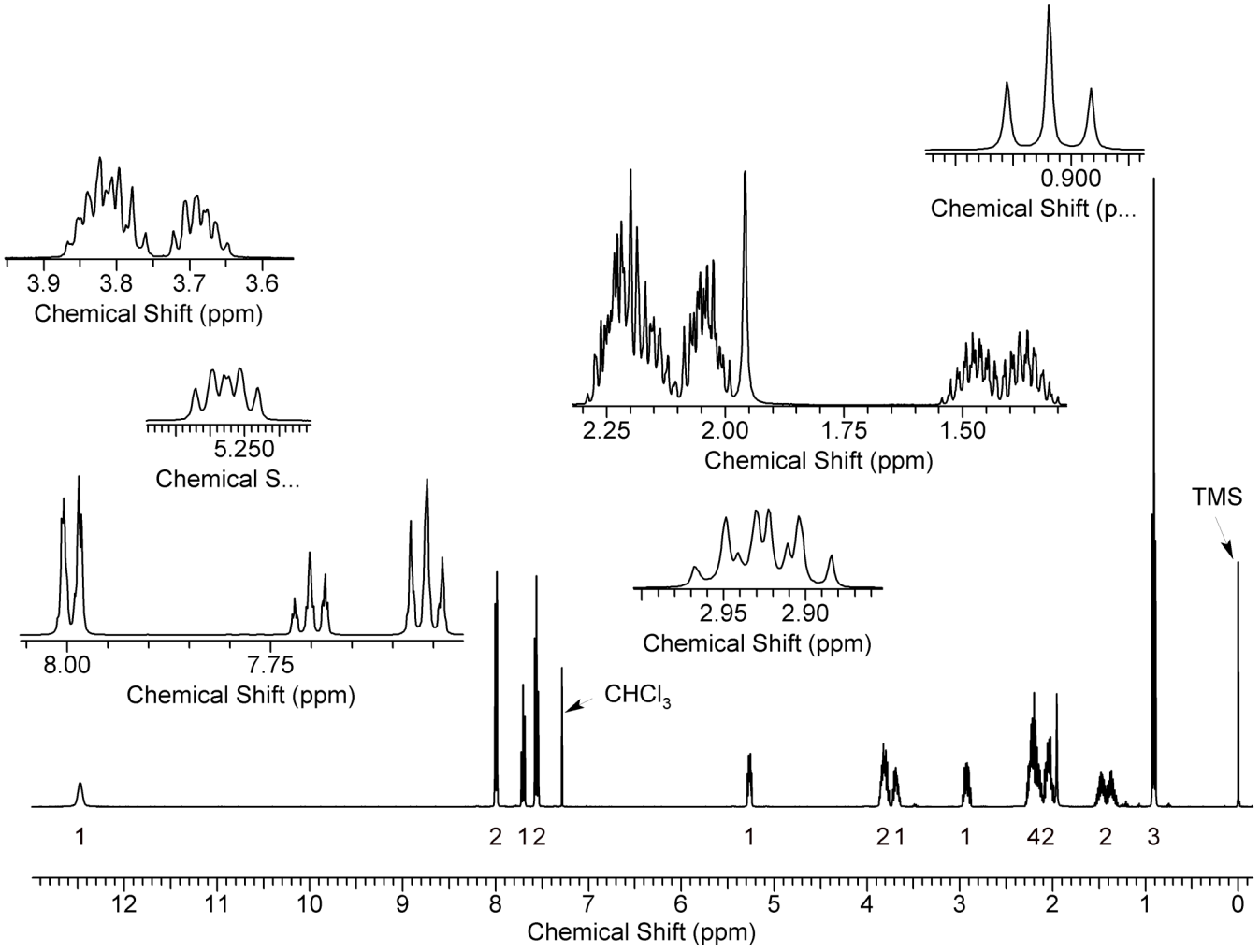
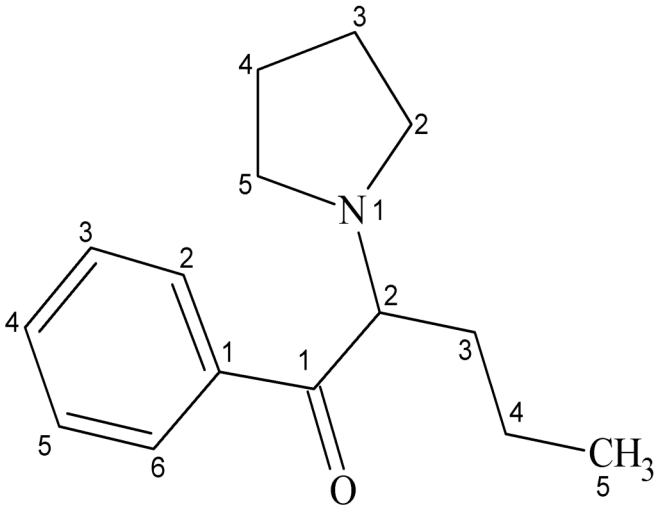


Figure 3 - ^{1}H and ^{13}C NMR data for α-pyrrolidinopentiophenone HCl

position	carbon (ppm)	proton (ppm)		J_{HH} (Hz)
Phenyl 1	137.1	-	-	
2,6	128.6	8.12	m	
3,5	128.4	7.45	m	
4	132.9	7.55	m	
1-Pentanone				
1	201.2	-	-	
2 (CH)	68.8	3.91	dd	8.9, 4.7
3	32.8	1.75, 1.91	m, m	
4	19.3	1.23, 12.9	m, m	
5	14.3	0.87	t	7.5
Pyrrolidine 1	-	-	-	
2,5	51.0	2.58, 2.68	m, m	
3,4	23.4	1.75, 1.91	m, m	
d = doublet, m = multiplet, t = triplet				



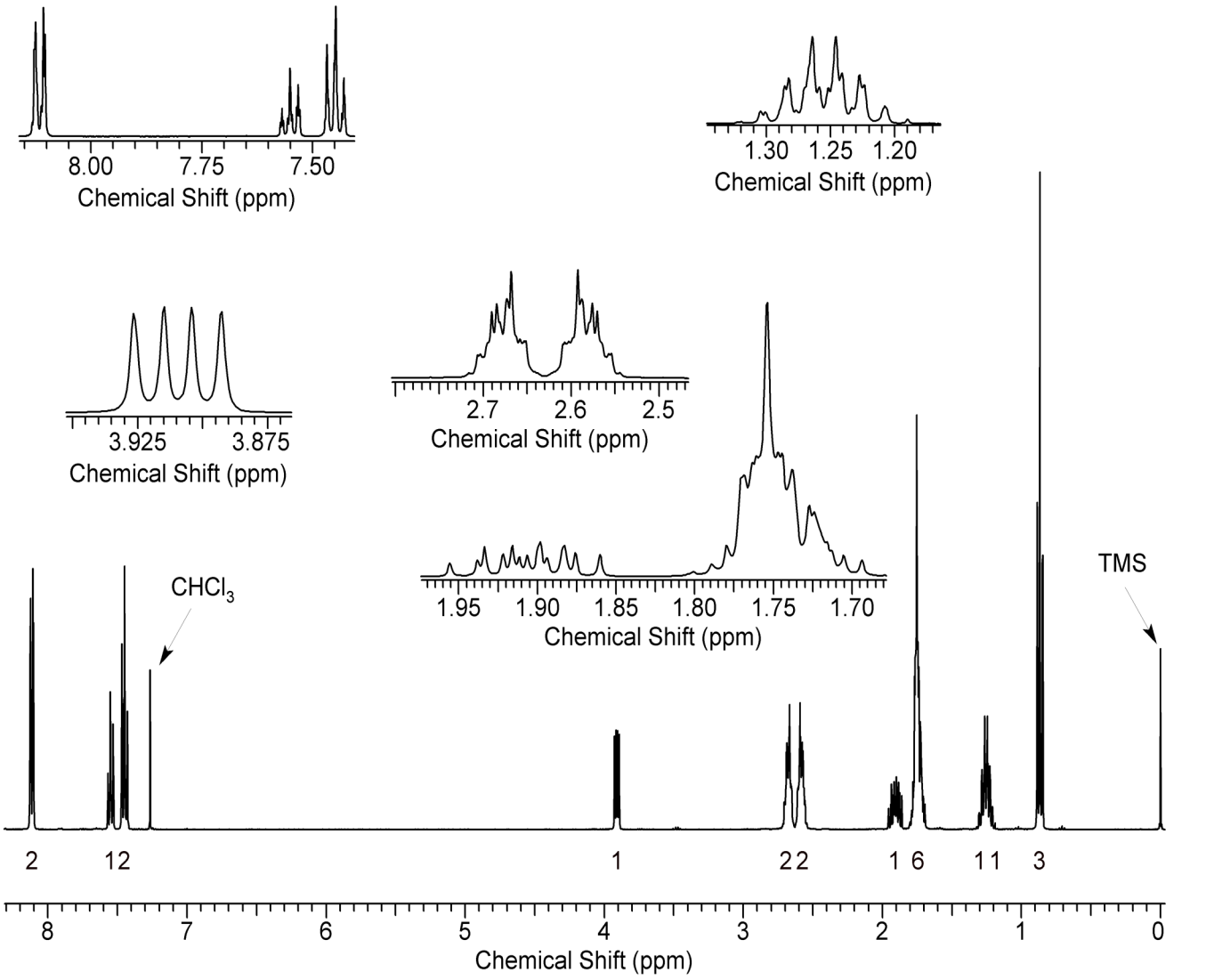


Figure 4 - ^{1}H and ^{13}C NMR data for α-pyrrolidinopentiophenone base.

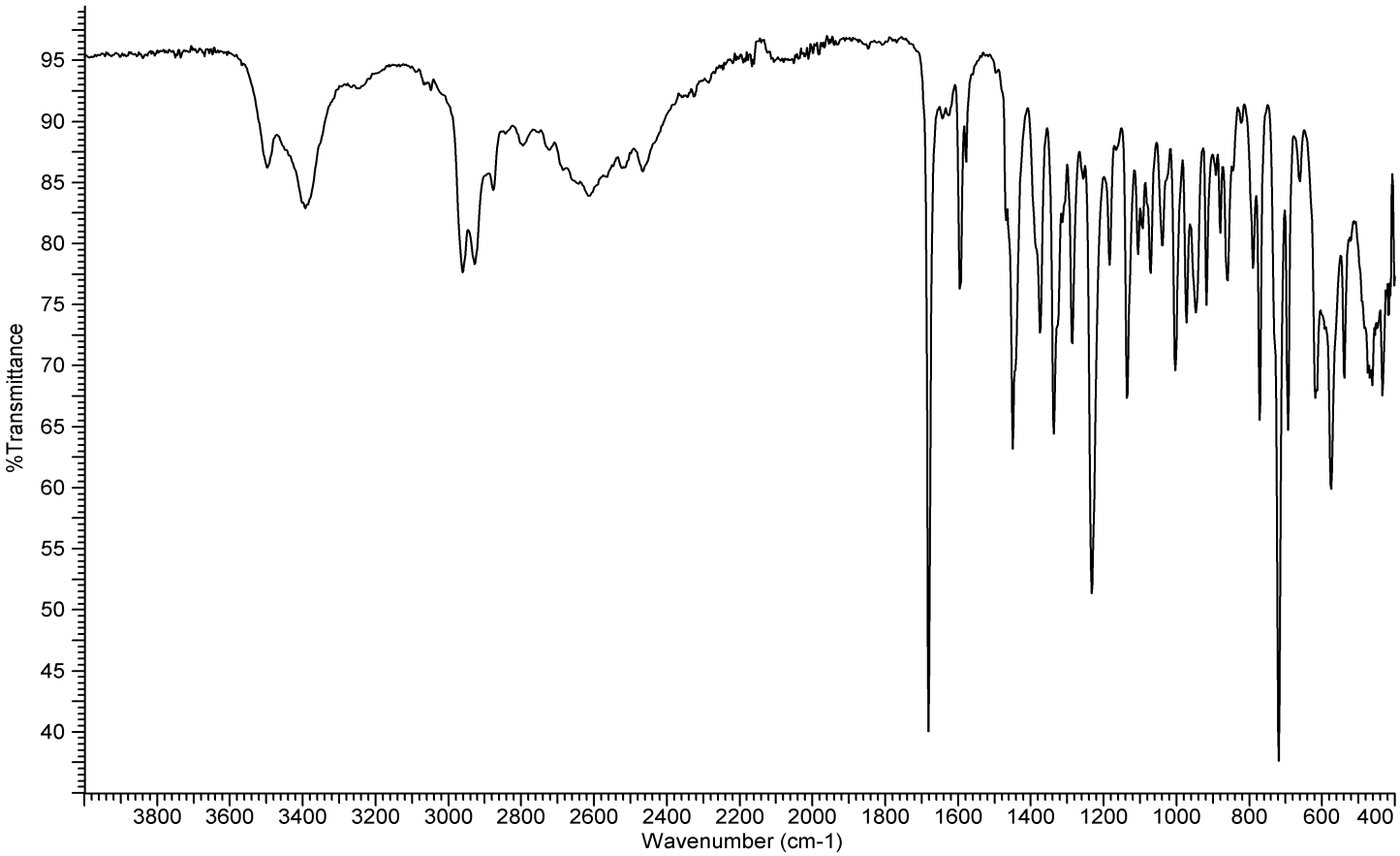


Figure 5 - FTIR of *α*-pyrrolidinopentiophenone HCl.

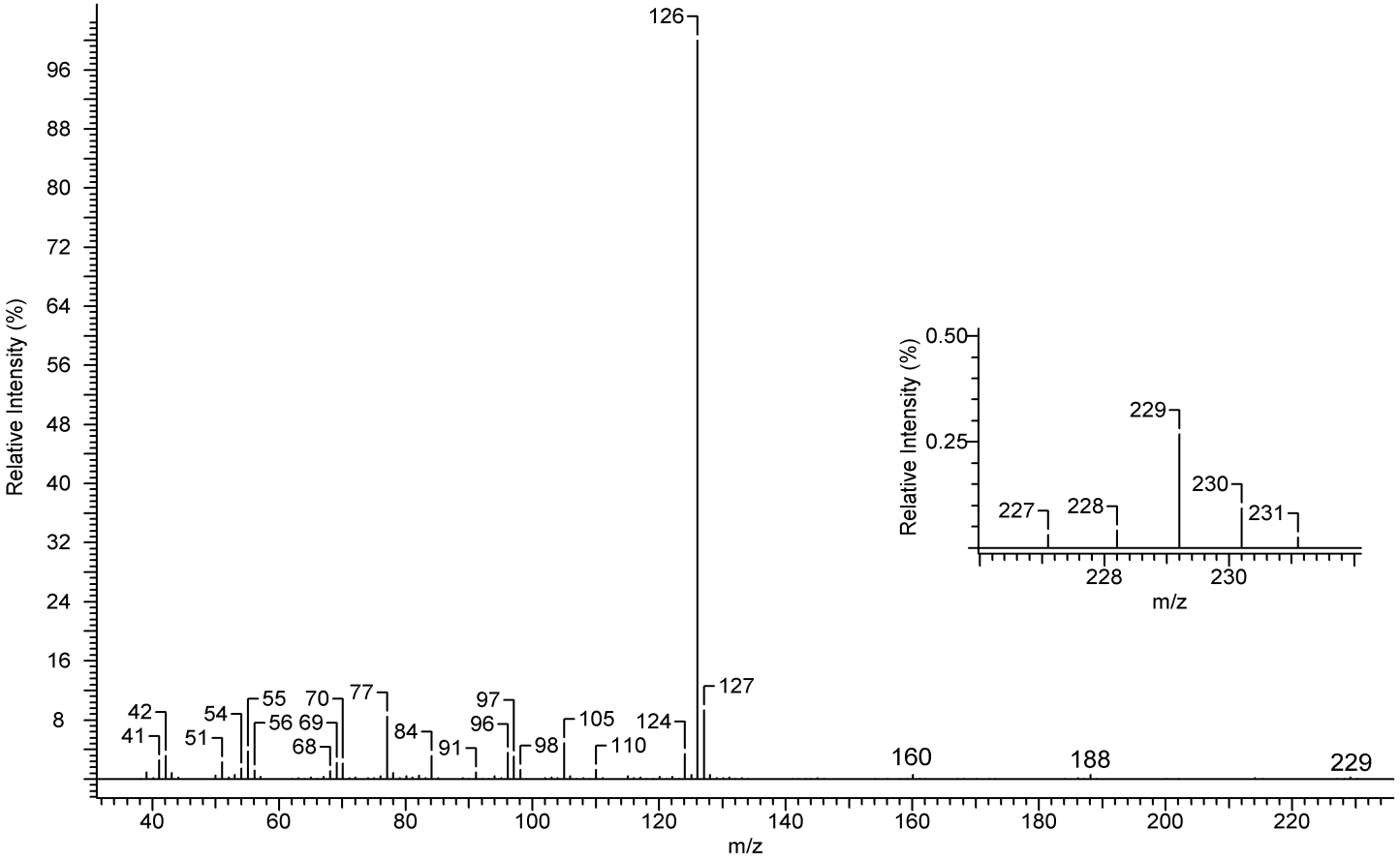


Figure 6 - Mass spectrum of *α*-pyrrolidinopentiophenone.

Conclusions

Analytical data are presented to assist forensic laboratories that encounter α-pyrrolidinopentiophenone in casework.

References

1. Sauer C, Peters FT, Haas C, Meyer MR, Fritschi G, Maurer HH. New designer drug α-pyrrolidionvalerophenone (PVP): Studies on its metabolism and toxicological detection in rat urine using gas chromatographic/mass spectrometric techniques. J. Mass Spectrom. 2009; 44(6):952-964.
2. Meltzer PC, Butler D, Deschamps JR, Madras BK. 1-(4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (pyrovalerone) analogs. A promising class of monoamine uptake inhibitors. J. Med. Chem. 2006;49(4):1420-1432.
3. Code of Federal Regulations. 21 U.S.C. § 802(32)(A).