The Characterization of 2-(5-Methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine (5-MeO-BFE) and Differentiation from its N-Ethyl Analog

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ABSTRACT: The synthesis, analysis, and characterization of 2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine (commonly referred to as "Head F--k"[1], "5-MeO-BFE", and "dimemebfe") and its N-ethyl analog are discussed. Analytical data (mass spectrometry, nuclear magnetic resonance spectroscopy, and infrared spectroscopy) are presented and compared.

KEYWORDS: 2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine, dimemebfe, 5-MeO-BFE, head f--k, 2-(5-methoxy-1-benzofuran-3-yl)-N-ethylethanamine, designer drug, synthesis, characterization, forensic chemistry.

2-(5-Methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine (Figure 1, structure **1**), is currently sold over the Internet as "Head F--k", and has become a popular "research chemical" for recreational drug use. Although not currently scheduled under the U.S. Controlled Substances Act, it may be considered to be an analog of the Schedule I drug 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) (Figure 1, structure **3**), with the indole nitrogen replaced with an oxygen to make a benzofuran [1]. This compound was first reported in 1992 to evaluate its affinity for serotonin receptors in rats and for possible use in the design of serotonin receptor ligands [2].

Herein, we report the synthesis and structural elucidation of **1** and its N-ethyl analog, 2-(5-methoxy-1-benzofuran-3-yl)-N-ethylethanamine (Figure 1, structure **2**). Analytical profiles (nuclear magnetic resonance spectroscopy, mass spectrometry, and infrared spectroscopy) of these compounds are presented and compared 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). 5-Methoxybenzofuran-yl-acetic acid was a product of Princeton Biomolecular Research (Monmouth Junction, NJ) and all other chemicals and NMR solvents were of reagent-grade quality and products of Aldrich Chemical (Milwaukee, WI).

Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were obtained on an Agilent VNMRS 600 MHz NMR using a Protune 5 mm broadband, variable temperature, pulse field gradient probe (Agilent, Palo Alto, CA). The samples were dissolved in deuterochloroform ($CDCl_3$) containing tetramethylsilane (TMS) and the 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, HMBC, and NOESY. Data processing and structure elucidation were performed using ACD Structure Elucidator software (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

[1]The letters "uc" have been removed to avoid problems with Internet firewalls.

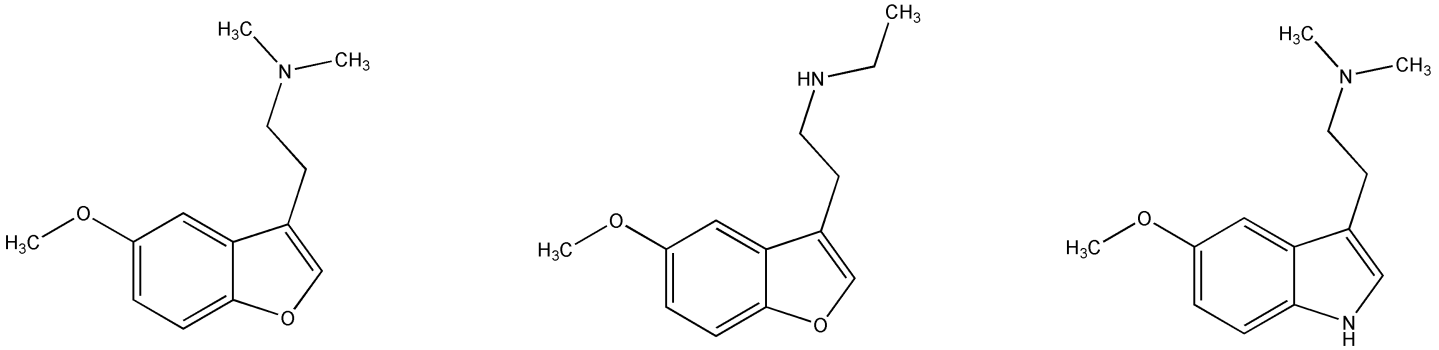
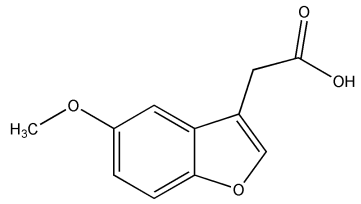
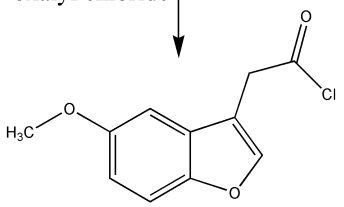


Figure 1 - Structural formulas of 2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine **1**, 2-(5-methoxy-1-benzofuran-3-yl)-N-ethylethanamine **2**, and 5-methoxy-N,N-dimethyltryptamine **3**.



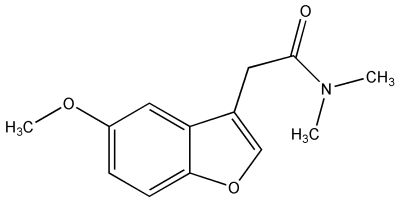
(5-methoxy-1-benzofuran-3-yl)acetic acid (**4**)

oxalyl chloride



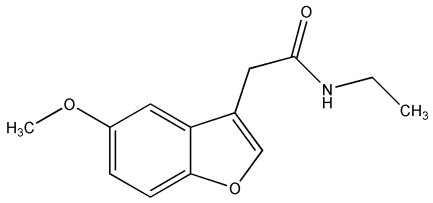
(5-methoxy-1-benzofuran-3-yl)acetyl chloride (**5**)

dimethylamine



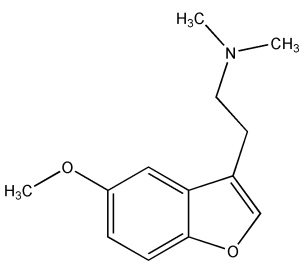
2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethylacetamide (**6**)

ethylamine



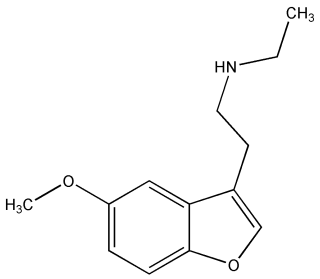
2-(5-methoxy-1-benzofuran-3-yl)-N-ethylacetamide (**7**)

LAH



2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine (**1**)

LAH



2-(5-methoxy-1-benzofuran-3-yl)-N-ethylethanamine (**2**)

Figure 2 - Synthetic route for 2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine and 2-(5-methoxy-1-benzofuran-3-yl)-N-ethylethanamine.

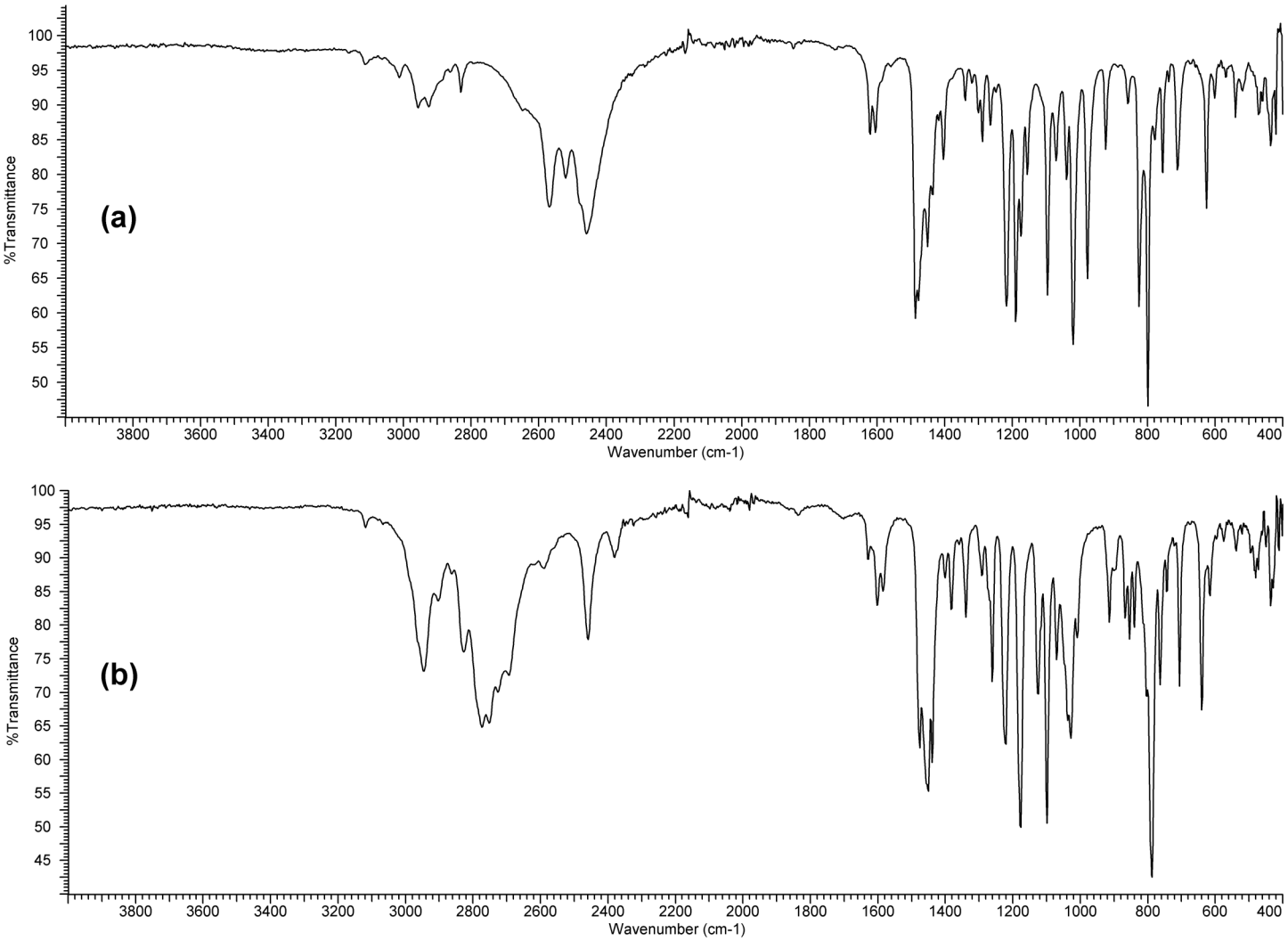


Figure 3 - Infrared spectrum of (**a**) 2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine HCl **1** and (**b**) 2-(5-methoxy-1-benzofuran-3-yl)-N-ethylethanamine HCl **2**.

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 2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethyl-ethanamine **1** and 2-(5-methoxy-1-benzofuran-3-yl)-N-ethyl-ethanamine **2**.*

In accordance with Journal policy, exact experimental details are not provided, but are outlined in Figure 2. Briefly, 5-methoxybenzofuran-3-yl-acetic acid **4** was converted to the acid chloride **5**, which was then reacted with dimethylamine or ethylamine to give the amides **6** and **7**, respectively. Amides **6** and **7** were then reduced with LAH to provide compounds **1** and **2**.

Results and Discussion

GC retention time data for compounds **1**, **2**, **3, 4**-TMS, **6**, and **7** are presented in Table 1. All amines were injected as the free base. Compounds **1** and **2** were easily resolved under the conditions utilized.

The FTIR spectra for **1** HCl and **2** HCl are illustrated in Figure 3. Comparison of the hydrochloride ion pairs reveals dissimilar absorption patterns with the most prominent differences being in the region of 2400-3000 cm^{-1}, which are attributed to the tertiary (compound **1**) *vs*. secondary (compound **2**) amine HCl ion-pairs. Significant variances are also found in the region of 600-1700 cm^{-1}.

Mass spectra for **1** and **2** are presented in Figure 4. The spectra produced from **1** (Figure 4a) and **2** (Figure 4b) gave a base peak at *m/z* 58 and a moderate molecular ion at *m/z* 219. However, **2** produces much more intense ions at *m/z* 161, *m/z* 162, and *m/z* 219, relative to **1** (*m/z* 161 is ~ 1.7X, *m/z* 162

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

Compound	R_t (min)
1	14.60
2	15.44
3	18.90
4-TMS	16.18
6	19.28
7	18.78

[a]Conditions given in the experimental section.

is ~10X, and *m/z* 219 is ~ 4X greater for **2**). Although the relative abundances for the remaining ions are quite similar, the two compounds are easily distinguished on the basis of the *m/z* 161/162 ratio (*m/z* 161/162 = 7.3:1 for compound **1** and *m/z* 161/162 = 1.1:1 for compound **2**). The ion produced at *m/z* 162 for **2** is analogous to hydrogen rearrangement (hydrogen migration from the nitrogen to the benzofuran moiety), followed by α-cleavage, as found for MDA and other related secondary amines [3].

The NMR assignments for the HCl ion-pairs dissolved in $CDCl_3$ of **1** and **2** are found in Figures 5 and 6. The aromatic proton and carbon spectra are very similar, with only slight chemical shift movement. The amine proton in **1** is a broad singlet at 12.84 ppm which integrates to 1, while the amine protons in **2** are at 9.94 ppm and integrate to 2. Both

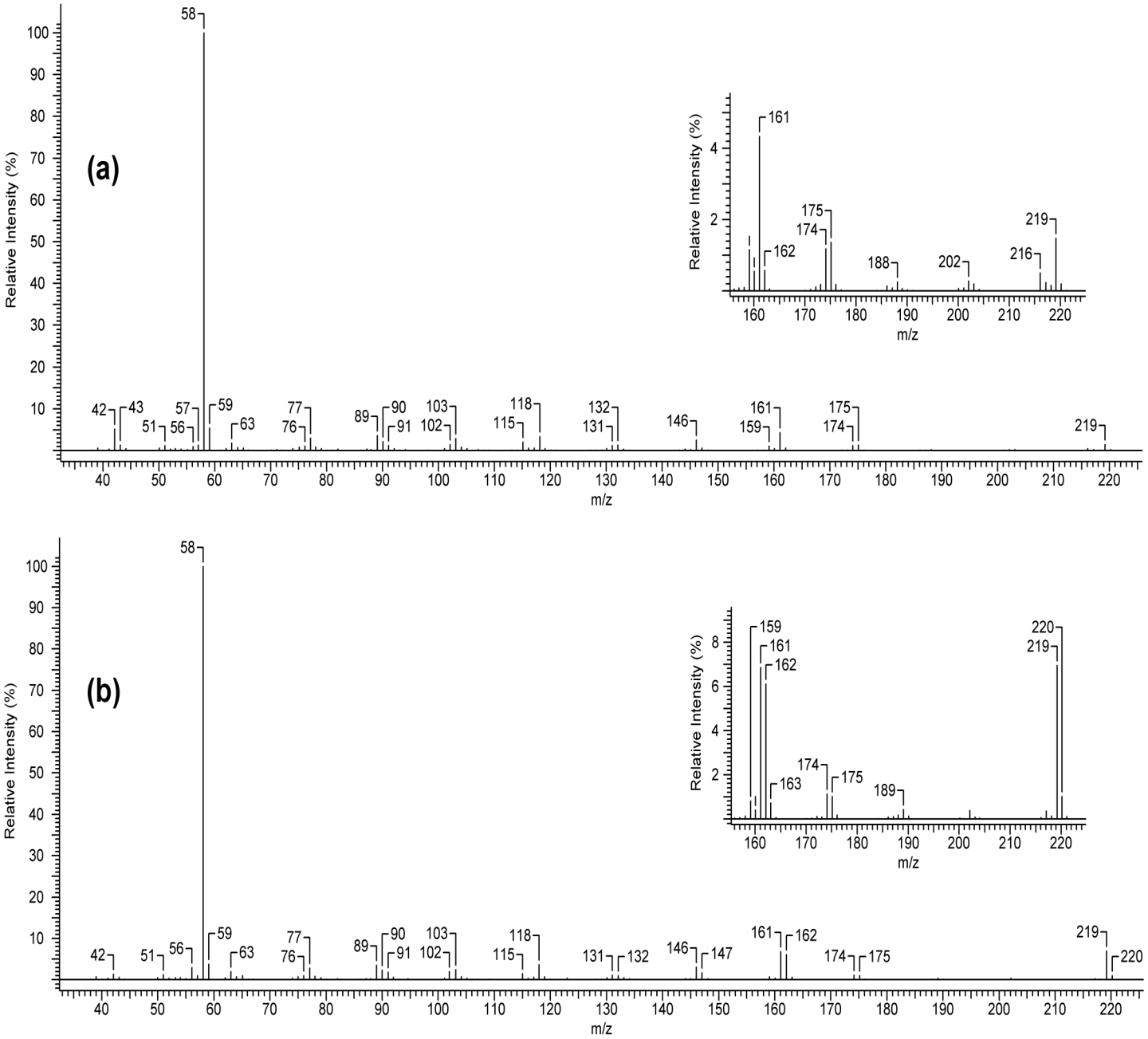
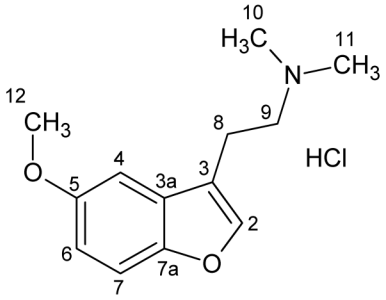
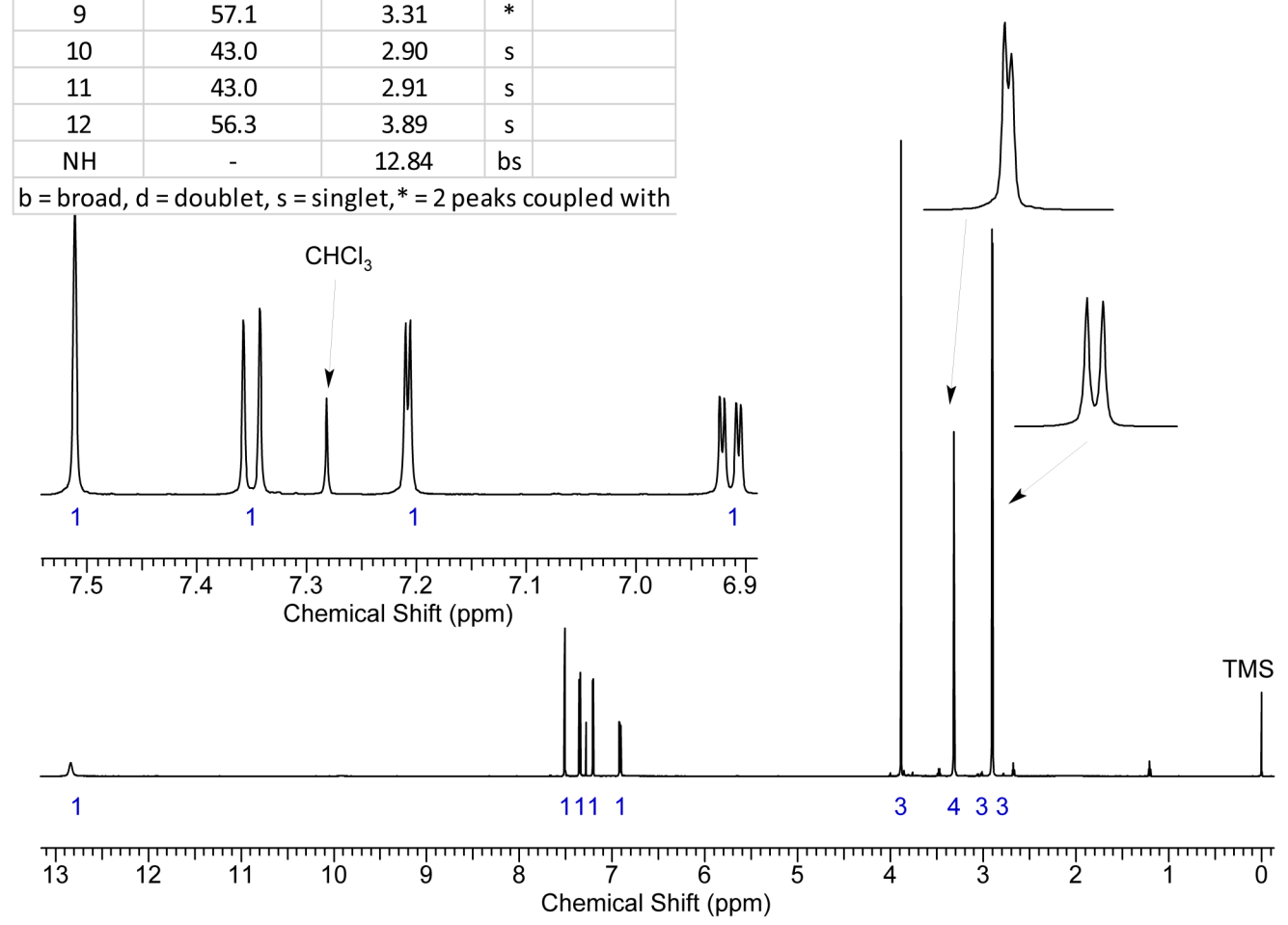


Figure 4 - Mass spectra of (**a**) 2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine **1** and (**b**) 2-(5-methoxy-1-benzofuran-3-yl)-N-ethylethanamine **2**.

position	Carbon (ppm)	Proton (ppm)		$J_{HH,HF}$ (Hz)
2	142.8	7.51	s	
3	114.8	-		
3a	127.4	-		
4	101.9	7.21	d	2.6
5	156.2	-		
6	113.8	6.91	dd	8.9, 2.6
7	112.2	7.35	d	8.9
7a	150.2	-		
8	19.6	3.31	*	
9	57.1	3.31	*	
10	43.0	2.90	s	
11	43.0	2.91	s	
12	56.3	3.89	s	
NH	-	12.84	bs	

b = broad, d = doublet, s = singlet,* = 2 peaks coupled with





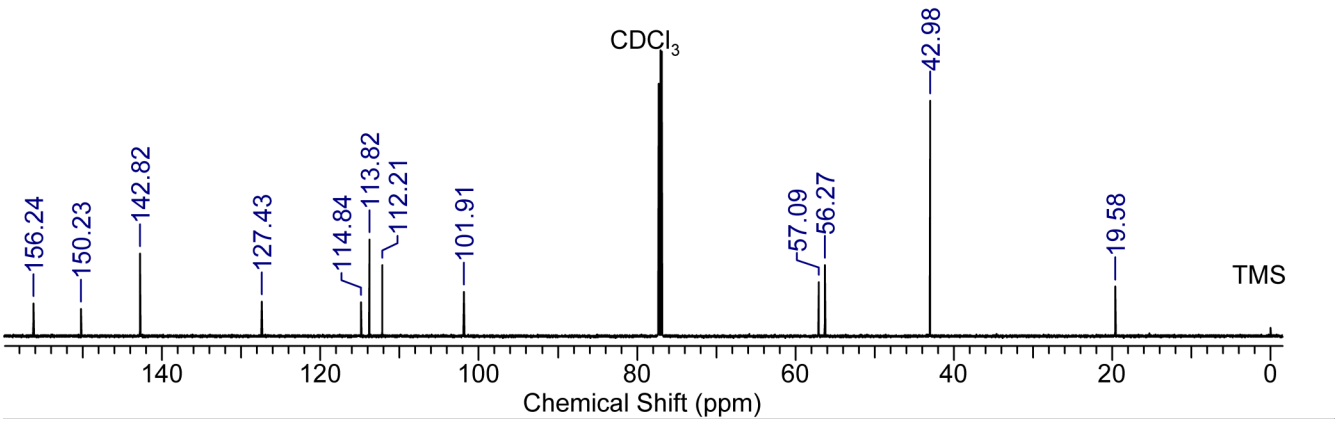
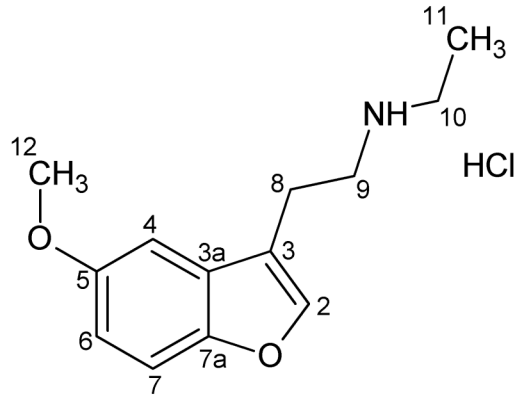


Figure 5 - ^{1}H and ^{13}C NMR data for 2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine HCl **1**.

position	Carbon (ppm)	Proton (ppm)		J_{HH} (Hz)
2	142.9	7.48	s	
3	115.3	-		
3a	127.6	-		
4	101.8	7.15	d	2.4
5	156.1	-		
6	113.6	6.88	dd	8.8, 2.4
7	112.1	7.32	d	8.8
7a	150.2	-		
8	20.8	3.37	m	
9	46.7	3.24	m	
10	43.0	3.11	m	
11	11.3	1.52	t	7.3
12	56.1	3.82	s	
NH	-	9.94	bs	
b = broad, d = doublet, m = multiplet, s = singlet, t = triplet				



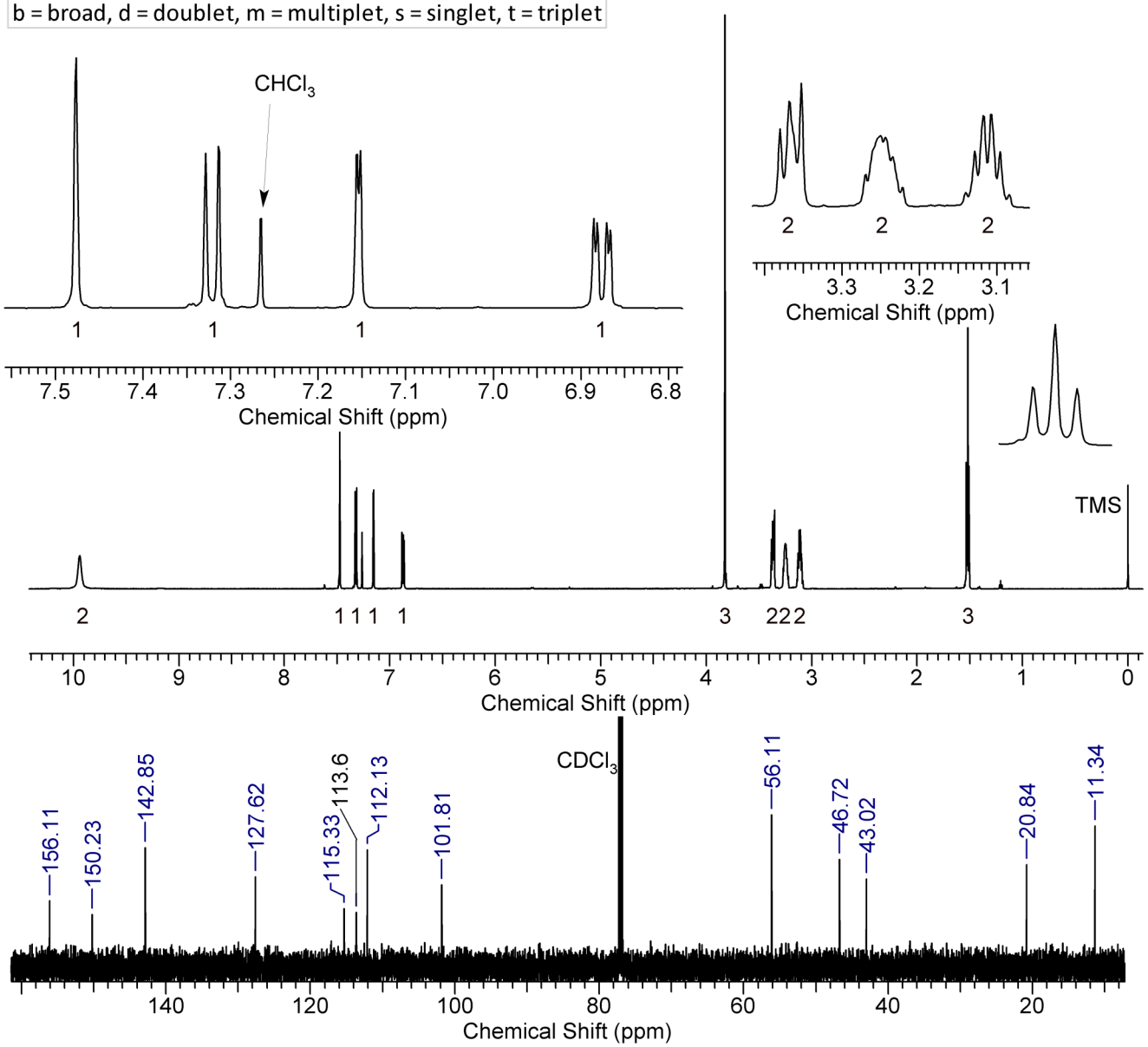


Figure 6 - ^{1}H and ^{13}C NMR data for 2-(5-methoxy-1-benzofuran-3-yl)-N-ethylethanamine HCl **2**.

compounds have a proton methoxy singlet at 3.8-3.9 ppm. The major spectral difference lies in the aliphatic region. The two methylenes appear as two peaks at 3.31 ppm ^{1}H (4 protons) in **1** due to severe 2nd order effects. Compound **2** methylenes appear as two proton multiplets at 3.24 and 3.37 ppm. Compound **1** has two methyl proton singlets at 2.90 and 2.91 ppm, while compound **2** has a two proton multiplet at 3.11 ppm and a methyl triplet at 1.52 ppm.

Conclusions

Analytical data are presented to assist forensic laboratories that encounter 2-(5-methoxy-1-benzofuran-3-yl)-N,N-dimethylethanamine in casework. Each of the three presented spectral techniques can provide unequivocal characterization.

References

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3. Smith RM. *Understanding Mass Spectra: A Basic Approach,* 2nd ed. John Wiley & Sons, Inc., Hoboken, NJ, 2004: 258-62.