The Characterization of 4- and 5-Iodo-2-aminoindan

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ABSTRACT: The synthesis, analysis, and characterization of 4- and 5-iodo-2-aminoindan (commonly referred to as "4-IAI" and "5-IAI") are discussed. Analytical data (mass spectrometry, nuclear magnetic resonance spectroscopy, and infrared spectroscopy) are presented and compared.

KEYWORDS: 5-iodo-2-aminoindan, 4-iodo-2-aminoindan, 2-aminoindan, 5-IAI, 4-IAI, 2-AI, designer drug, synthesis, characterization, forensic chemistry.

The Special Testing and Research Laboratory recently received a request to characterize (and eventually synthesize) an unknown compound in a suspected drug exhibit. The exhibit consisted of approximately 300 grams of a tan powder containing ascorbic acid as a diluent. The compound of interest was suspected as being 5-iodo-2-aminoindan, based partially on a mass spectrum exhibiting an apparent molecular ion of *m/z* 259. This molecular weight was consistent with a new compound, 5-iodo-2-aminoindan, currently advertised for sale over the Internet. We synthesized both 4- and 5-iodo-2-aminoindan for structural elucidation and eventual confirmatory analyses at our laboratory.

5-Iodo-2-aminoindan (Figure 1, structure **1**), commonly referred to as "5-IAI," is a relatively new compound for sale over the Internet. The IUPAC name for 5-IAI is 5-iodo-2,3-dihydro-1*H*-inden-2-amine. Although not currently scheduled under the U.S. Controlled Substances Act, it may be considered to be an analog of amphetamine [1] (Figure 1, Structure **3**); with linkage of amphetamine's terminal methyl with the *ortho* position of the aromatic ring, to form an indan ring system. 5-IAI was first synthesized and reported in 1991 to study its pharmacological effects and evaluated for neurotoxicity [2,3] and a recent review on aminoindanes addressed the need for analytical profiles as well as the significant challenges in identifying these new "legal highs" [4].

Herein, we report the synthesis and structural elucidation of 5-IAI **1** and its positional isomer, 4-iodo-2-aminoindan (4-IAI) **2**. 4-IAI is not yet available for purchase on the Internet. Analytical profiles (nuclear magnetic resonance, mass spectrometry, and infrared spectroscopy) of these compounds and their synthetic intermediates and impurities are presented and compared to assist forensic chemists who may encounter these substances in casework.

Experimental

Chemicals, Reagents, and Materials

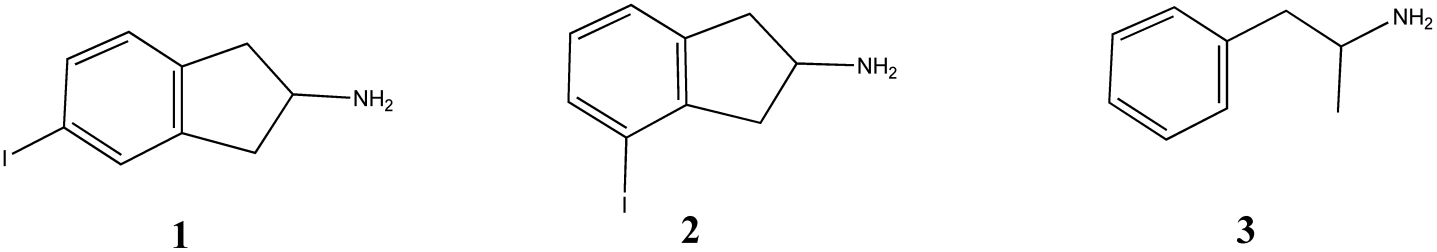
All solvents were distilled-in-glass products of Burdick and Jackson Labs (Muskegon, MI). 2-Aminoindan and all other chemicals and NMR solvents were of reagent-grade quality and products of Aldrich Chemical (Milwaukee, WI).

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.

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 HCl salt of the compound was initially dissolved in deuterium oxide (D_2O) containing 0.05% v/v TSP as the 0 ppm reference compound, and later base extracted using saturated sodium bicarbonate into $CDCl_3$ containing TMS. The sample temperature was maintained at 26°C. Standard Agilent pulse sequences were used to collect the following spectra: Proton, carbon (proton decoupled), and



1 **2** **3**

Figure 1 - Structural formulas of (**1**) 5-IAI, (**2**) 4-IAI, and (**3**) amphetamine.

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).

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 5- and 4-IAI

In accordance with Journal policy, exact experimental details are not provided, but are outlined in Figure 2. Briefly, 2-aminoindan (2-AI) **4** was converted to the N-trifluoroacetyl derivative **5**, which was then iodinated to give a mixture of the 5-iodo-2-aminoindan-TFA derivative **6** and the 4-iodo-2-aminoindan-TFA derivative **7**. Compounds **6** and **7** were separated via column chromatography (silica gel) and then deprotected to provide **1** and **2**, respectively.

Results and Discussion

Structural Elucidation/Confirmation of 5- and 4-IAI

Proton and carbon NMR spectra as well as the assignments for 5-IAI are presented in Figure 3 (HCl salt in D_2O) and Figure 4 (base in $CDCl_3$). The NMR spectra and assignments for 4-IAI base are found in Figure 5. Assignments were based on proton chemical shifts and peak patterns, carbon chemical shifts, HSQC (1 bond carbon to proton correlations), and HMBC (2-4 bond carbon to proton correlations correlations). Assignments were further confirmed using ACD Structure Elucidator software.

NMR spectra confirmed both the 4- and the 5-IAI structures. There are 9 carbons: 3 aromatic quaternary carbons (one with the exceptionally low chemical shift, C-5 at 91-95 ppm, bonded to iodine), 3 aromatic protonated carbons (the proton peak patterns indicating a CH=CH-C=CH- sequence for the 5-iodo and a CH=CH-CH sequence for the 4-iodo compound), 2 aliphatic methylenes (almost identical in carbon and proton chemical shifts for the 5-iodo compound and very different chemical shifts for the 4-iodo compound), and 1 aliphatic methine. The methine and 2 methylene proton peak patterns

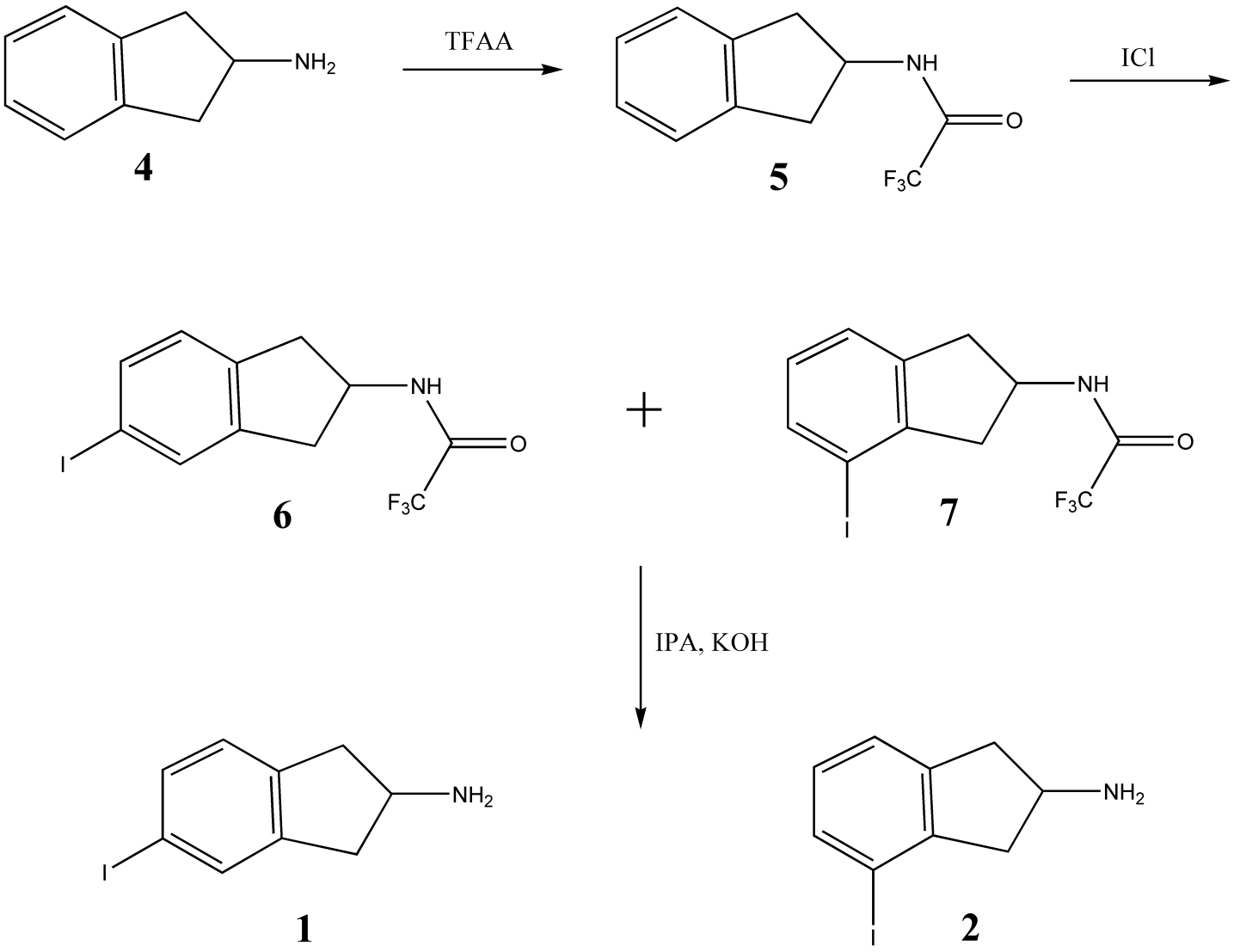
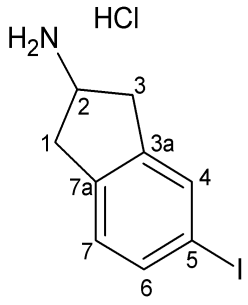


Figure 2 - Synthetic route for 5-IAI **1** and 4-IAI **2**.

indicate CH_2-CH-CH_2 bonding with the methine likely bonded to nitrogen (51-54 ppm carbon). The carbons of the two methylenes in the 5-iodo compound are nearly equivalent, making assignment of protons to carbons initially difficult; however, due to the lack of 2nd order effects, and due to the coupling constants present, the two protons at 3.0 ppm (base spectrum) are not bonded to the same carbon, and the two protons at 3.4 ppm (base spectrum) are not bonded to the same carbon. The 5-iodo compound methylene carbons have both a 3.0 ppm proton and a 3.4 ppm proton (base spectrum). The cause of these nearly equivalent signals is the nearly symmetric appearance of the molecule. In the 4-iodo compound, there is no axis of symmetry and the methylene protons and carbons are quite far apart.

The mass spectra for 5-IAI, 4-IAI, and 2-AI are illustrated in Figure 6. Both 5-IAI and 4-IAI gave an intense molecular ion at *m/z* 259 and are easily distinguished by the relative intensities of ions found at *m/z* 115, 117, 130, and 132. Additionally, the

Solvent: D_2O with TSP

Position	Carbon (ppm)	Proton (ppm, J)	Structure
1	39.8	3.02 dd(17.3, 3.5 Hz), 3.39 dd(17.3, 7.3 Hz)	
2	54.3	4.18 tt(7.3, 3.5 Hz)	
3	39.8	3.05 dd(17.3, 3.5 Hz), 3.43 dd(17.3, 7.3 Hz)	
3a	144.8	-	
4	136.7	7.75 bs	
5	94.8	-	
6	139.1	7.66 bd(7.8 Hz)	
7	129.7	7.15 d(7.8 Hz)	
7a	142.0	-	
		b = broad, d = doublet, t = triplet, s = singlet	

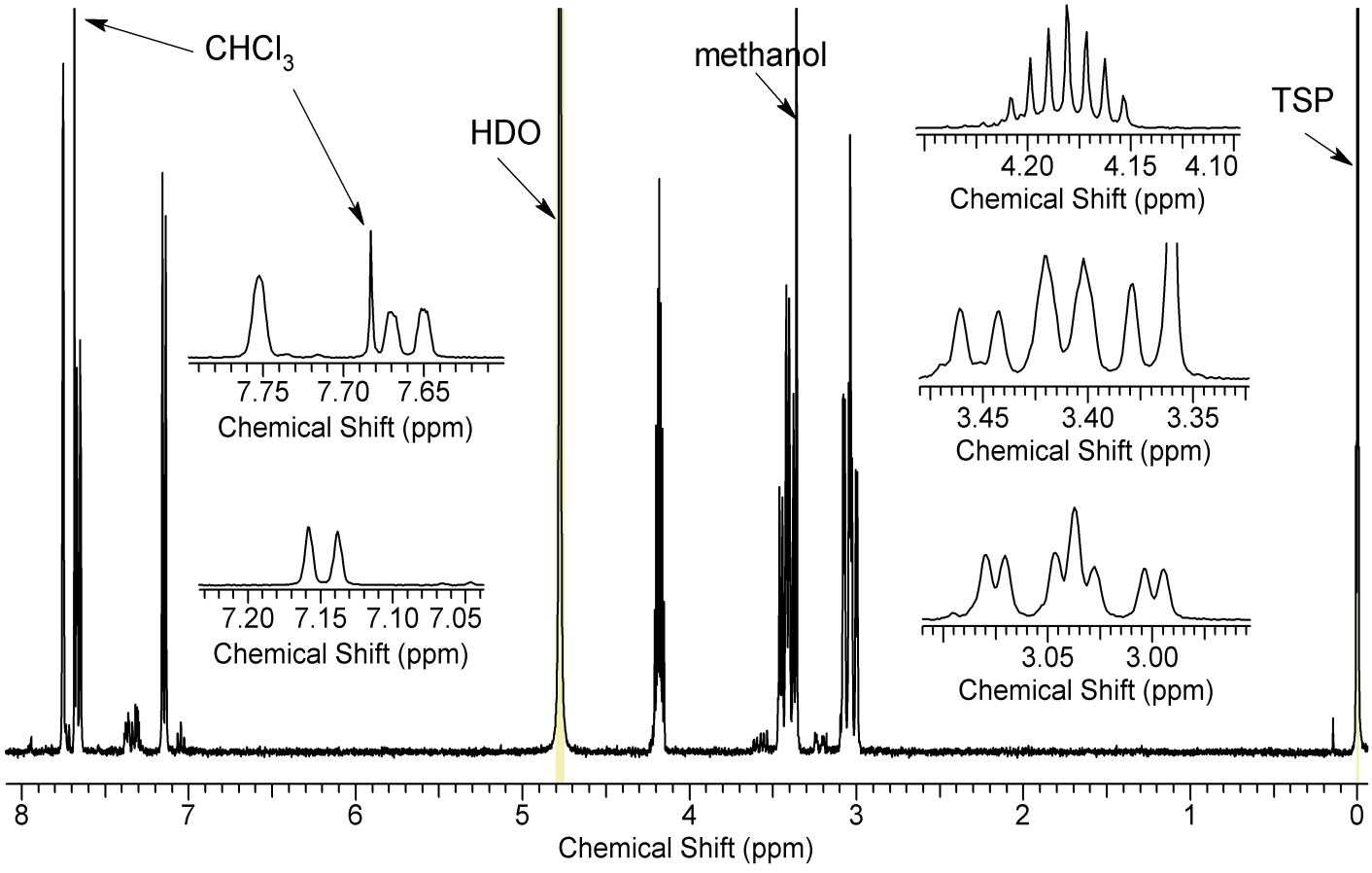


Figure 3 - ^{1}H and ^{13}C NMR data for 5-IAI HCl **1**.

molecular ion for 5-IAI (*m/z* 259) is the base peak, while the base peak for 4-IAI is found at *m/z* 132 (5-IAI produces *m/z* 132 as a minor ion).

The FTIR spectra for 5-IAI, 4-IAI, and 2-AI are illustrated in Figure 7 as their HCl ion pairs. Comparison of the hydrochloride ion pairs of 5- and 4-IAI reveals very similar absorption patterns with only minor band shifts in the region of 500-1750 cm^{-1}. 2-AI is easily distinguished from the iodinated derivatives. Since the spectra of 5- and 4-IAI are very similar, additional or supplementary spectroscopic methods should be utilized for identification.

Illicit Sample

A partial reconstructed total ion chromatogram of the basic extract of the sample is illustrated in Figure 8. GC retention time data for the respective compounds are presented in Table 1, along with the synthetic intermediates. Peak #1 was identified as 2-AI and was present at a trace level. Peak #2

Solvent: $CDCl_3$ with TMS (D_2O/sodium bicarbonate extraction of HCl salt)

Position	Carbon (ppm)	Proton (ppm, J)	Structure
1	42.7	2.62 dd(14.9, 4.8 Hz), 3.12 dd(14.9, 6.7 Hz)	
2	~53.0 *	3.16 tt(6.7, 4.8 Hz)	
3	42.9	2.66 dd(14.9, 4.8 Hz), 3.16 dd(14.9, 6.7 Hz)	
3a	144.6	-	
4	133.9	7.55 bs	
5	~91.4 *	-	
6	135.4	7.47 bd(8.2 Hz)	
7	126.8	6.97 d(8.2 Hz)	
7a	~141.6 *	-	
		b = broad, d = doublet, t = triplet, s = singlet	
		* = carbon value derived from HMBC	

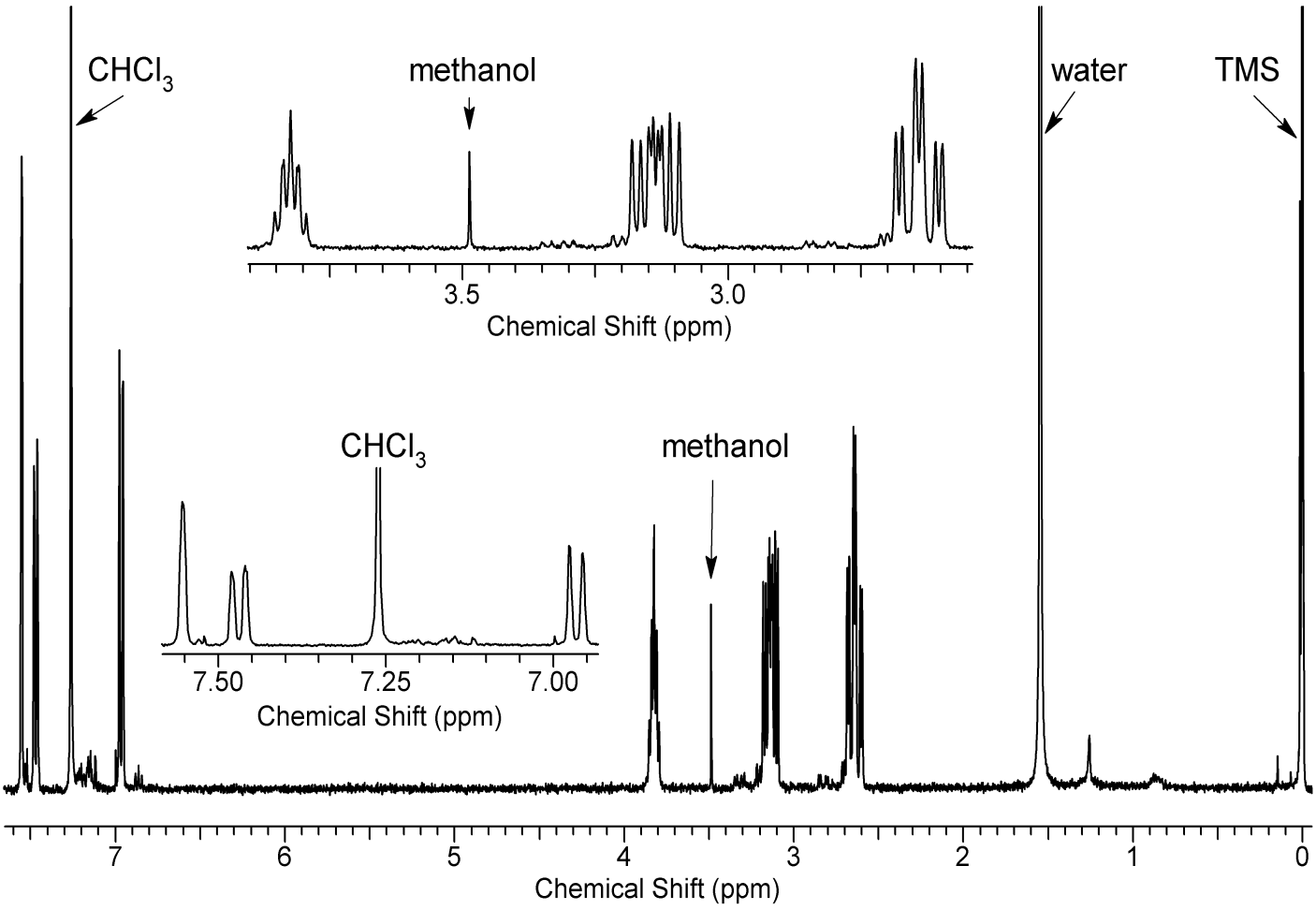


Figure 4 - ^{1}H and ^{13}C NMR data for 5-IAI base **1**.

represented approximately one percent of the ion current and produced an identical mass spectrum to synthesized 4-IAI. Peak #3 constituted approximately 92 percent of the ion current and produced an identical mass spectrum to synthesized 5-IAI. Peak #4 produced a base peak at *m/z* 115 and a molecular ion and *m/z* 285 (mass spectrum not illustrated), respectively, and could not be identified. Peak #5 produced a mass spectrum (Figure 9) with a molecular ion at *m/z* 293 and a M+2 isotope abundance ratio consistent with mono-chloro substitution.

A mass of 293 Daltons with an apparent chlorine substitution suggests the compound is a chloro-iodo-2-aminoindan; however, the exact position of substitutions is not known (Figure 10). A chloro-iodo-2-aminoindan would be an expected by-product from the use of iodine monochloride (ICl) as an iodination reagent. Peaks #6-9 each produced a mass spectrum (Figure 11) with a molecular ion at *m/z* 385; these are

Solvent: $CDCl_3$ with TMS

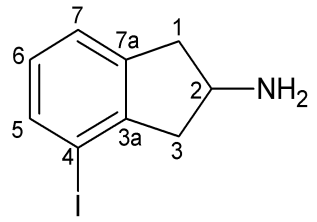
Position	Carbon (ppm)	Proton (ppm, J)	Structure
1	44.6	2.82 dd(16.0, 4.9 Hz), 3.32 dd(16.0, 6.9 Hz)	
2	51.3	3.84 tt(6.9, 4.9 Hz)	
3	48.5	2.68 dd(16.6, 4.9 Hz), 3.18 dd(16.6, 6.9 Hz)	
3a	146.5	-	
4	94.2	-	
5	135.8	7.54 d(7.9 Hz)	
6	128.4	6.86 dd(7.9, 7.4 Hz)	
7	124.5	7.15 d(7.4 Hz)	
7a	142.6	-	
		b = broad, d = doublet, t = triplet, s = singlet	
		* = carbon value derived from HMBC	

Figure 5 - ^{1}H and ^{13}C NMR data for 4-IAI base **2**.

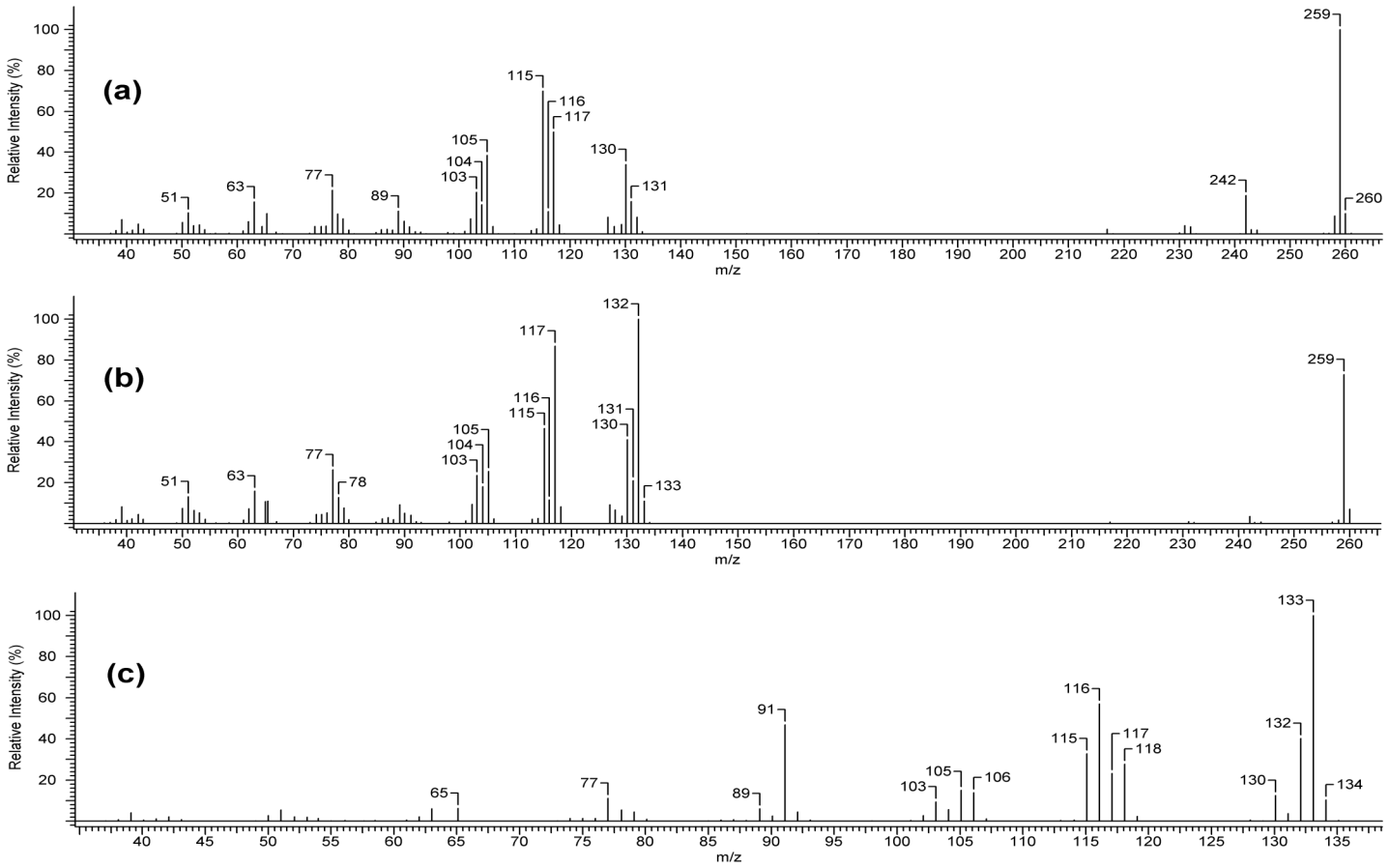


Figure 6 - Electron ionization mass spectra of (**a**) 5-IAI **1**, (**b**) 4-IAI **2**, and (**c**) 2-AI **4**.

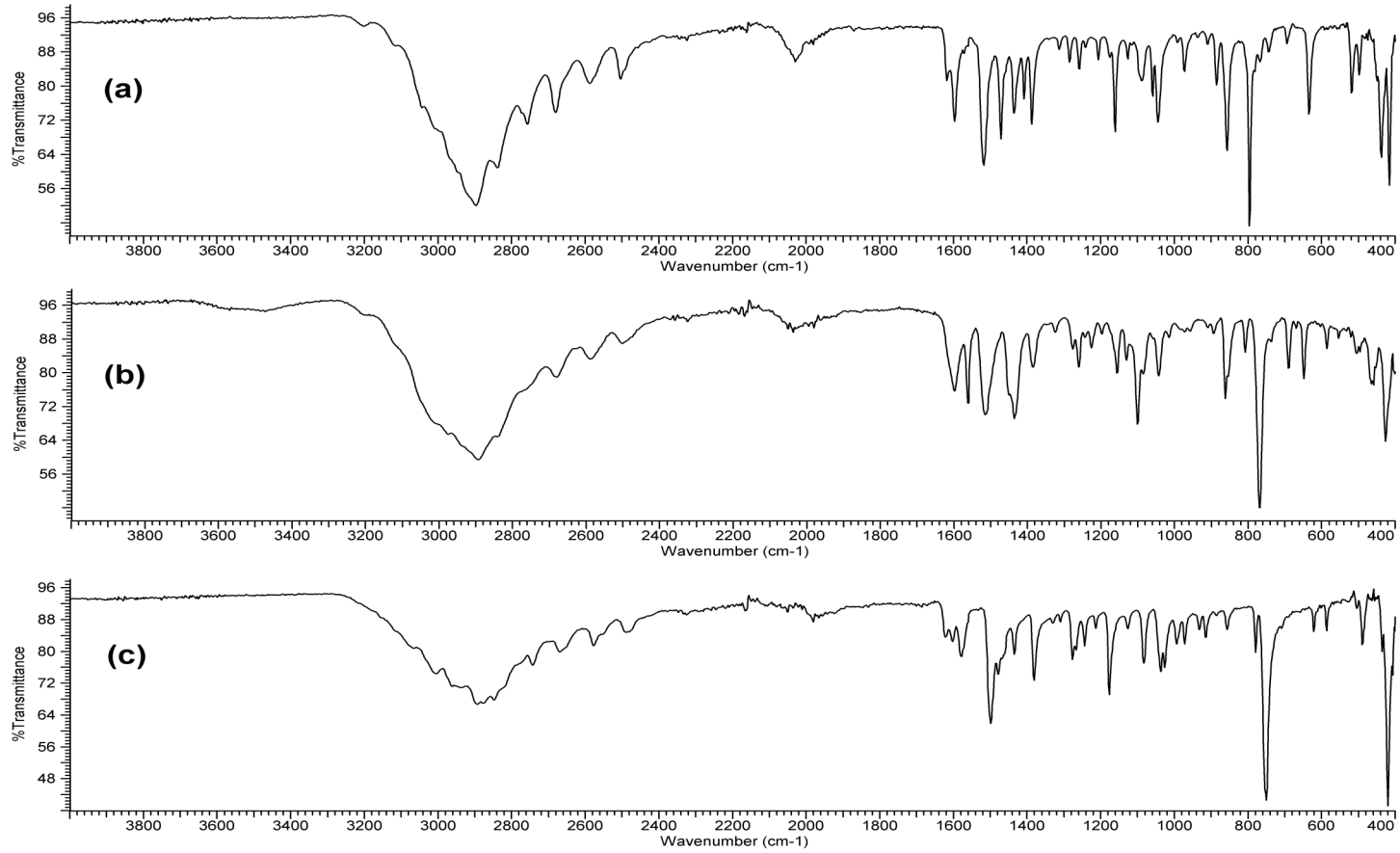


Figure 7 - Infrared spectrum of (**a**) 5-IAI **1**, (**b**) 4-IAI **2**, and (**c**) 2-AI **4**.

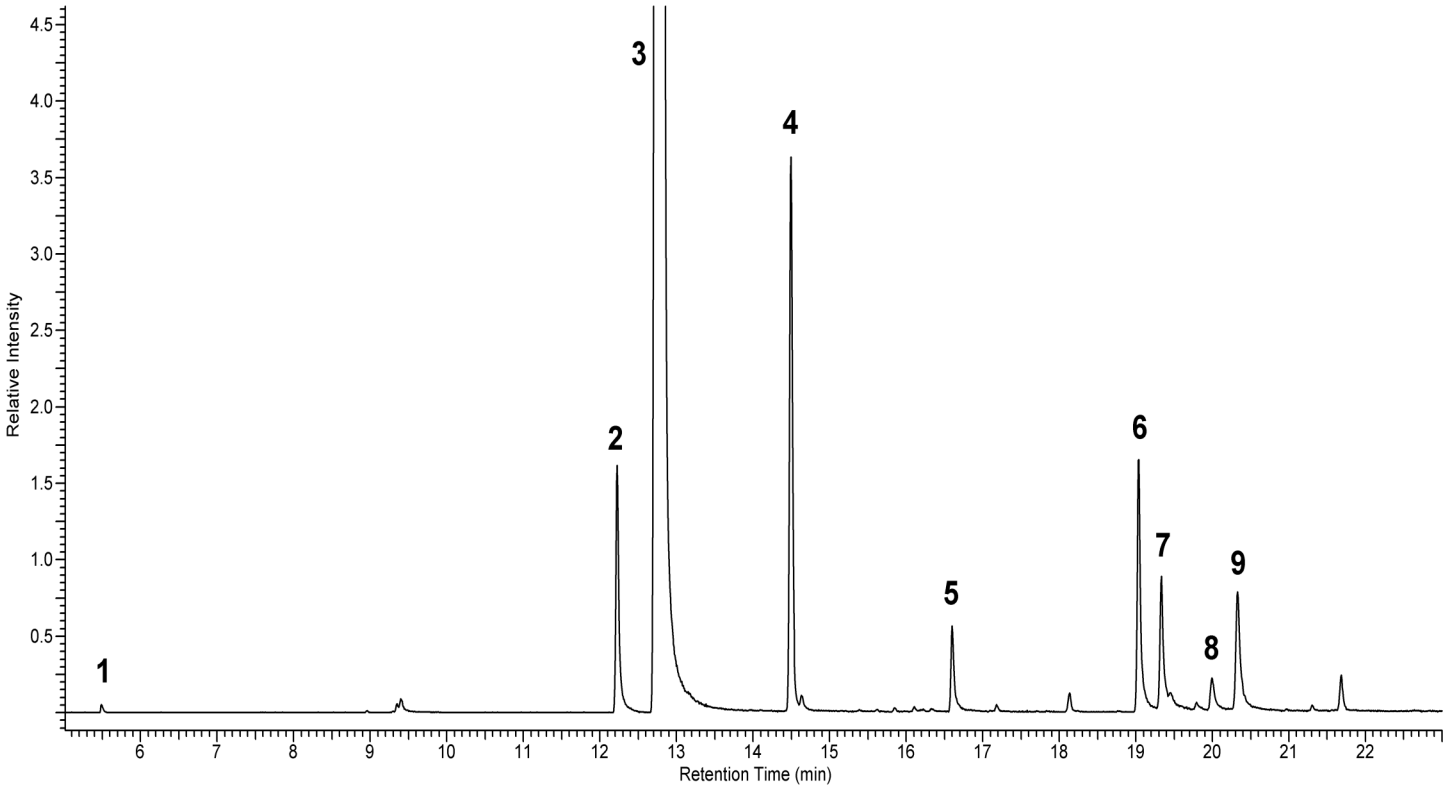


Figure 8 - Reconstructed total ion chromatogram of a basic extract of the illicit 5-IAI sample. Peak identification: **1** = 2-AI, **2** = 4-IAI, **3** = 5-IAI, **4** = unknown compound, **5** = suspected iodo-chloro-2-aminoindan, and **6-9** = suspected di-iodo-2-aminoindans.

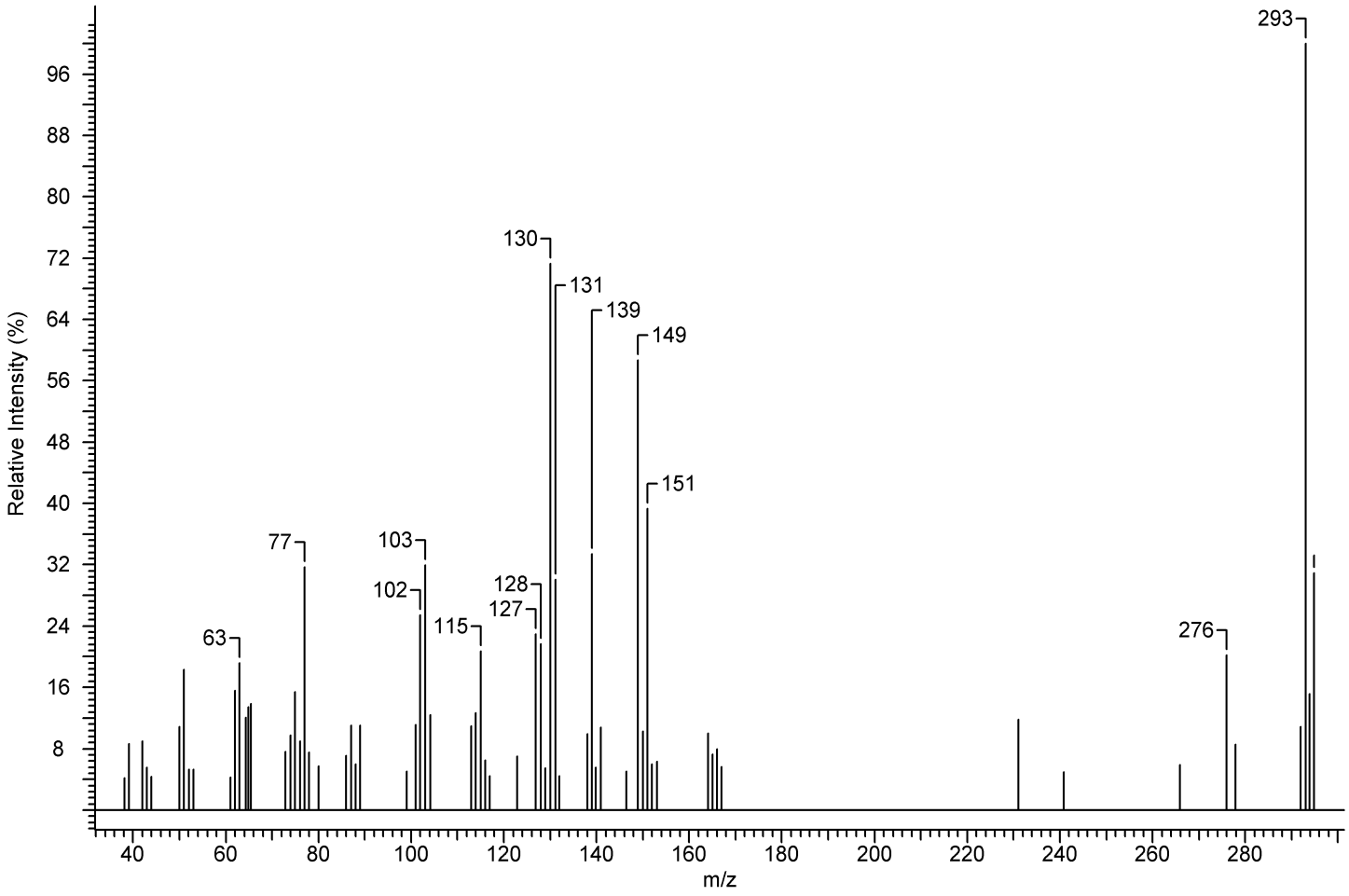


Figure 9 - Electron ionization mass spectrum of suspected chloro-iodo-2-aminoindan.

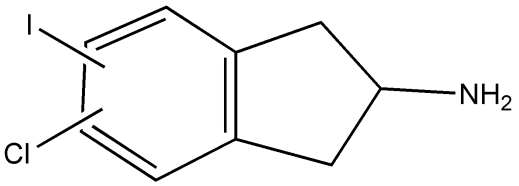


Figure 10 - Proposed structure of illicit synthesis by-product (chloro-iodo-2-aminoindan).

consistent with di-iodo-substituted 2-aminoindans; their proposed structures are given in Figure 12. Di-iodo-substituted 2-aminoindans would be expected by-products from the use of excess iodination reagent.

Conclusions

Analytical data are presented to assist forensic laboratories that encounter 4- and/or 5-IAI in casework. Care must be employed when utilizing FTIR for characterization. Both mass spectral and NMR techniques can provide unequivocal characterization of 4- versus 5-IAI.

Table 1 - Gas chromatographic retention times (R_t) for the iodo-2-aminoindans and related compounds[a].

Compound	R_t (min)
2-aminoindan	5.46
2-aminoindan-TFA derivative	8.55
4-iodo-2-aminoindan	12.22
5-iodo-2-aminoindan	12.74
4-iodo-2-aminoindan-TFA derivative	15.17
5-iodo-2-aminoindan-TFA derivative	15.87
proposed chloro-iodo-2-aminoindan	16.60
proposed di-iodo-2-aminoindan	19.03
proposed di-iodo-2-aminoindan	19.34
proposed di-iodo-2-aminoindan	20.00
proposed di-iodo-2-aminoindan	20.33

[a]Conditions given in the experimental section.

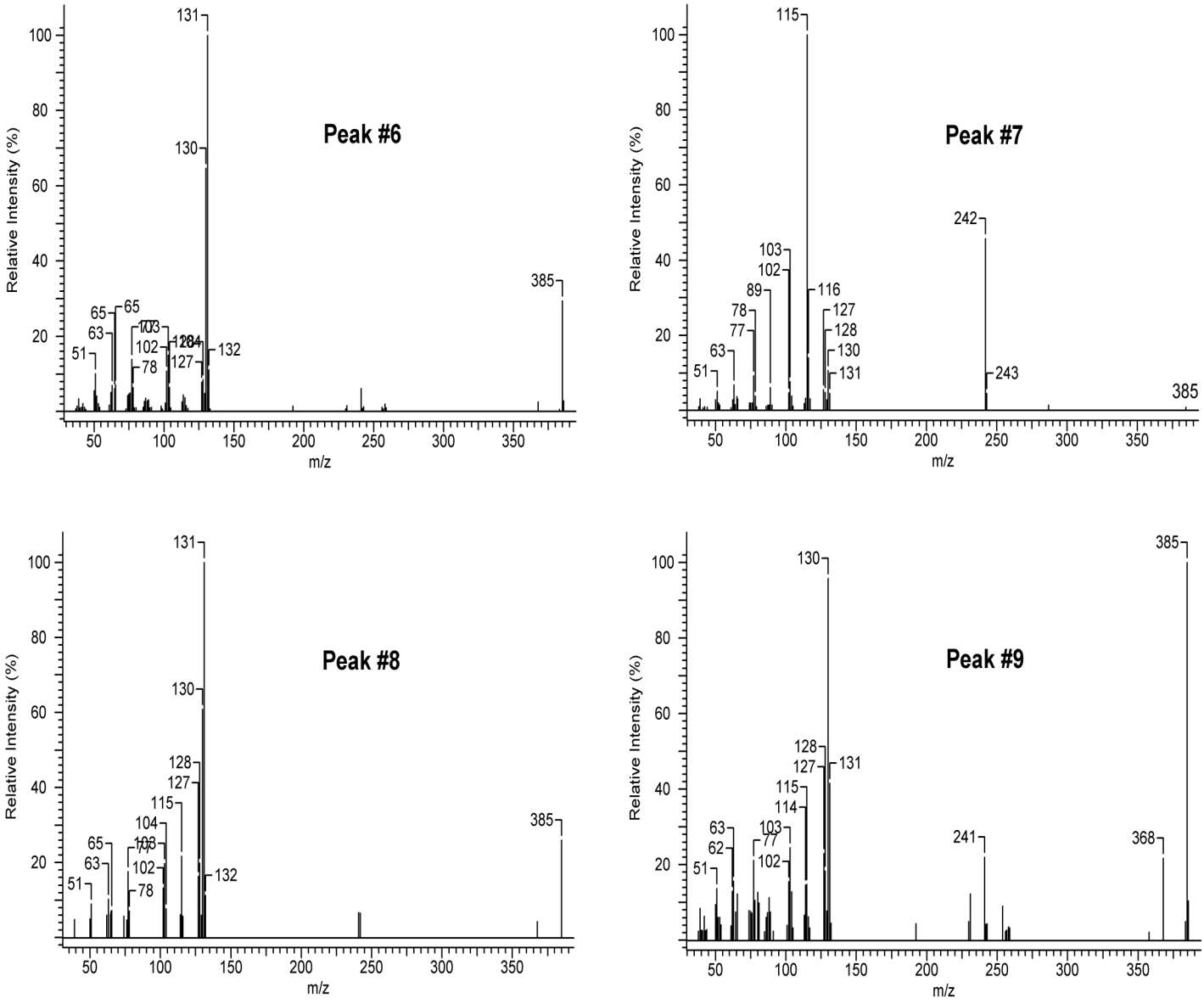


Figure 11 - Electron ionization mass spectra of suspected di-iodo-2-aminoindans.

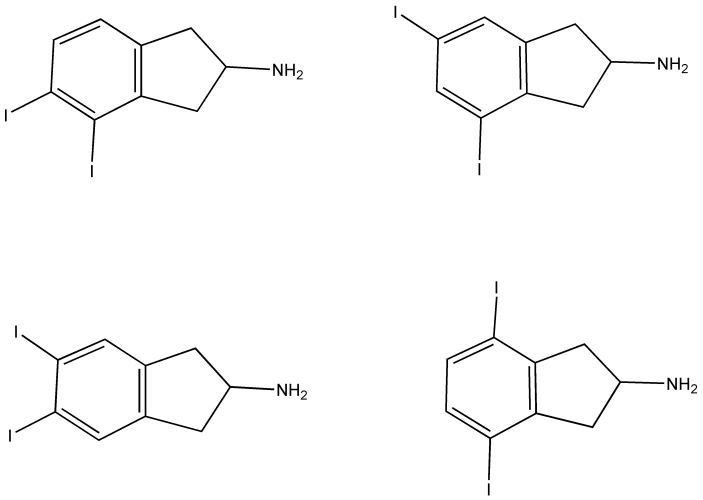


Figure 12 - Proposed structures of illicit synthesis by-products (di-iodo-2-aminoindans).

References

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