Differentiation of 3,4-Dimethylmethcathinone (3,4-DMMC) from its Dimethyl Aryl-Positional Isomers

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ABSTRACT: The synthesis and characterization of six dimethylmethcathinones via mass spectrometry, infrared spectroscopy, and nuclear magnetic resonance spectroscopy are discussed. Analytical data are presented to differentiate these positional analogues.

KEYWORDS: 3,4-dimethylmethcathinone, 2,3-dimethylmethcathinone, 2,4-dimethylmethcathinone, 2,5-dimethylmethcathinone, 3,5-dimethylmethcathinone, 2,6-dimethylmethcathinone, DMMC, designer drug, synthesis, characterization, forensic chemistry.

A number of methcathinone analogues have been recently reported in the literature [1-9]. The characterization of 3,4-dimethylmethcathinone (3,4-DMMC) has been reported [1], however, there are several structural analogues of 3,4-DMMC. Structural analogues are usually easily differentiated by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy; however, the majority of forensic laboratories are not equipped with such instrumentation, and therefore rely heavily on gas chromatography/mass spectrometry (GC/MS) and Fourier Transform infrared spectroscopy (FTIR) for the identification of drug exhibits. In many cases, GC/MS and/or FTIR do not always produce clear differentiation of structurally related analogues; therefore, standards are needed for direct comparison of spectra and retention data. Hence, we report the synthesis, characterization, and differentiation of five of the six dimethylmethcathinones (Figure 1, structures **5**-**9**) via mass spectrometry and infrared spectroscopy, and the trace-level synthesis and GC/MS analysis of the sixth dimethylmethcathinone (structure **10**). Only a trace amount of suspected **10** could be synthesized due to the effects of steric hindrance; therefore, only mass spectral data is presented for that isomer.

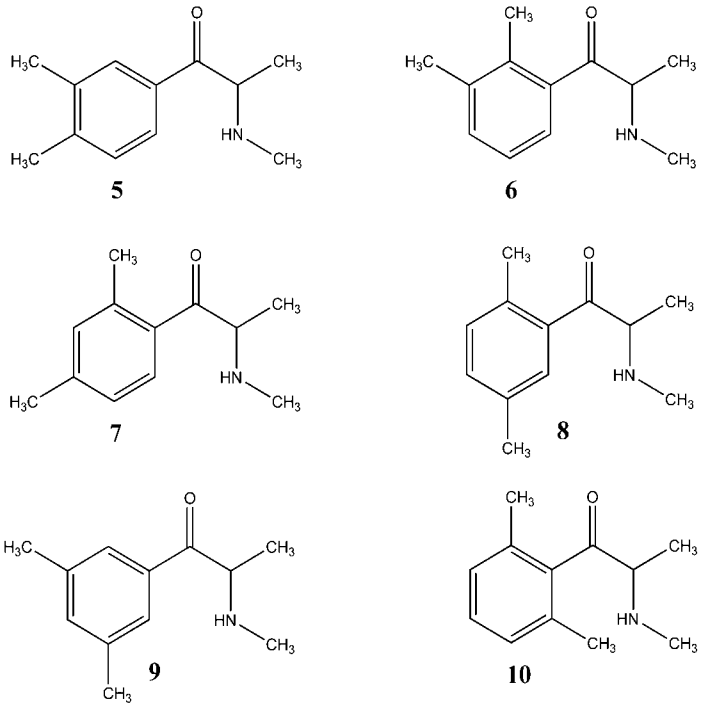

Figure 1 - Structural formulas. **5** = 3,4-dimethylmethcathinone, **6** = 2,3-dimethylmethcathinone, **7** = 2,4-dimethylmethcathinone, **8** = 2,5-dimethylmethcathinone, **9** = 3,5-dimethylmethcathinone, **10** = 2,6-dimethylmethcathinone.

Experimental

Chemicals, Reagents, and Materials

All solvents were distilled-in-glass products of Burdick and Jackson Labs (Muskegon, MI). 1-(2,3-Dimethylphenyl)propan-1-one, 1-(2,4-dimethylphenyl)propan-1-one, 1-(2,5-dimethylphenyl)propan-1-one, and 1-(3,5-dimethylphenyl)propan-1-one were products of Novel Chemical Solutions (Crete, NE). All other chemicals and NMR solvents were of reagent-grade quality and products of Sigma-Aldrich Chemical (Milwaukee, WI).

*Synthesis of 3,4-Dimethylmethcathinone **5***

In accordance with *Journal* policy, exact experimental details are not provided, but are outlined in Figure 2. Briefly, dimethylbromobenzene **1** was reacted with magnesium metal to give the Grignard **2**, which was added to propionitrile to give the ketone **3**, which was converted to the α-bromoketone **4**, which was reacted with methylamine to give 3,4-dimethylmethcathinone **5**, which was finally converted to its HCl ion-pair.

*Synthesis of the 2,3-, 2,4-, 2,5-, and 3,5-Dimethylmethcathinones **6, 7, 8,** and **9**.*

Each compound was synthesized using the appropriate dimethyl-substituted phenyl-1-propanone (analogous to **3**) using the route illustrated in Figure 2.

*Synthesis of 2,6-Dimethylmethcathinone **10***

Several attempts to produce **10** through three different routes were unsuccessful due to the effects of steric hindrance from the 2,6-dimethyl substitution. One synthetic route produced a trace amount of suspected desired material (determined via GC/MS), but there was insufficient material for NMR

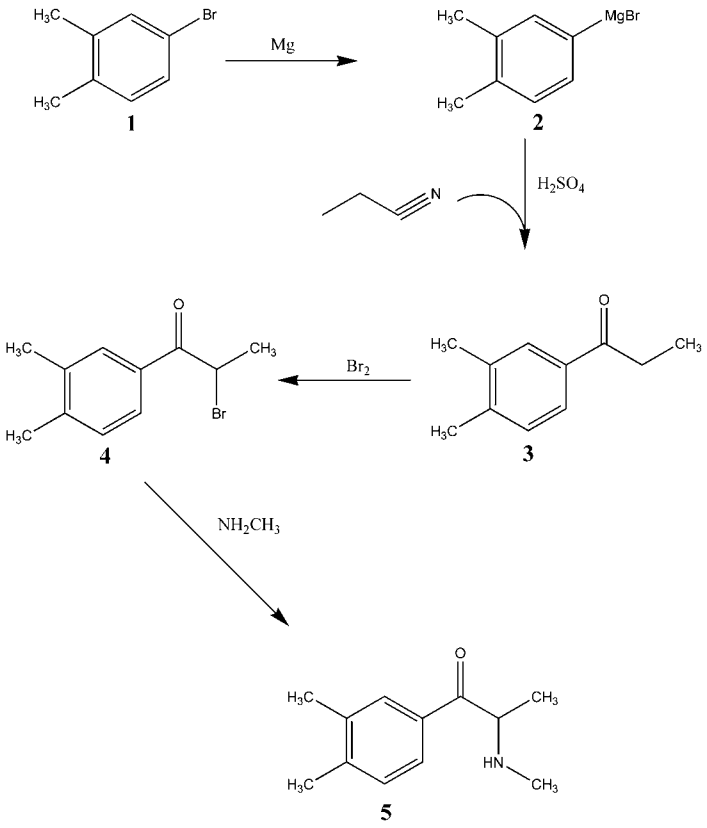

Figure 2 - Synthetic scheme for 3,4-dimethylmethcathinone **5**.

confirmation or an FTIR spectrum, and its identity is therefore unconfirmed.

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.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Proton (^1H), carbon (^{13}C), HSQC, and HMBC NMR spectra were obtained using an Agilent 400MR NMR with 5 mm Protune indirect detection, pulse field gradient probe (Palo Alto, CA) using standard Agilent pulse sequences. The compounds were extracted into deuterochloroform ($CDCl_3$) containing 0.03% v/v tetramethylsilane (TMS) using sodium bicarbonate saturated deuterium oxide (D_2O) (Sigma-Aldrich, St. Louis, MO). The sample temperature was maintained at 26°C. Data processing and structure elucidation were performed using Agilent NMR software and ACD Structure Elucidator software (Applied Chemistry Development, Toronto, Canada).

Table 1 - Gas Chromatographic Retention Times (min) for the dimethylmethcathinones[a].

Compound	R_t (min)
5	11.65
6	10.64
7	10.34
8	9.99
9	10.76
10[b]	9.78

[a]Conditions given in the experimental section.
[b] Trace material and structure not confirmed by NMR.

Results and Discussion

GC-MS and FTIR Differentiation of 3,4-DMMC from the 2,3-, 2,4-, 2,5-, 3,5- and (presumed) 2,6-positional analogues

GC retention time data for the respective compounds (Figure 1) are presented in Table 1. All amines were injected as their free bases. All six compounds were resolved in the described system.

Mass spectra and infrared spectra for compounds **5-10** are given in Figures 3-8 (except the FTIR for **10**).

The mass spectra of all six dimethylmethcathinones gave relatively similar fragmentation patterns, but significant differences were observed. Each produced a base peak at *m/z* 58 and a weak molecular ion at *m/z* 191. Compound **5** produced ion abundances of *m/z* 119 > *m/z* 115, while compounds **6-10** produced ion abundances of *m/z* 115 > *m/z* 119. Additionally, compound **5** was easily distinguished from **6**, **8**, **9**, and **10** by the relative abundances of ions at *m/z* 105 and *m/z* 133, where *m/z* 133 > *m/z* 105. Other significant differences between the spectra of **5-10** were also observed at low abundance ions between *m/z* 146 and *m/z* 176; each compound can be differentiated by its total spectrum.

The FTIR spectra for **5-9** gave somewhat similar secondary amine HCl ion-pair absorbances between 2400-3000 cm^{-1} as well as a ketone stretch at 1680-1700 cm^{-1}. However, characteristic differences were observed between 400-1600 cm^{-1}, where each compound could be easily differentiated.

NMR Characterization/Differentiation

Proton chemical shifts, peak patterns, coupling constants, and assignments are presented in Table 2. Carbon chemical shifts and assignments of the base forms are presented in Table 3. Assignments were based on proton chemical shifts and peak patterns, carbon chemical shifts, HSQC (1 bond carbon to proton), and HMBC (2-4 bond carbon to proton) spectra, and were further confirmed using ACD Structure Elucidator software.

For each compound, a $CH\text{-}CH_3$ group is shown by a methine quartet (3.93-4.19 ppm) coupled to a methyl doublet (1.19-

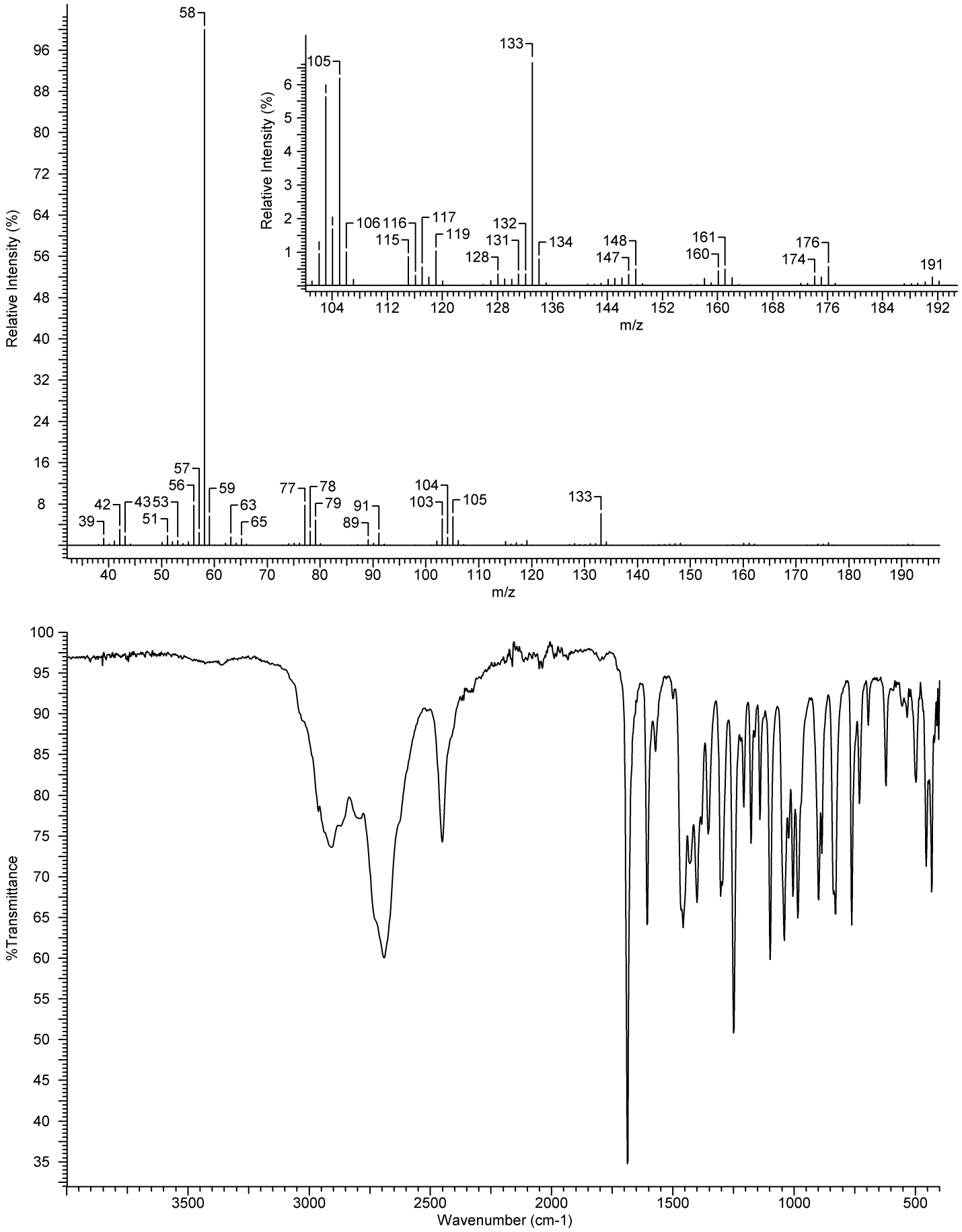

Figure 3 - Mass spectrum (upper) and of FTIR (lower) of 3,4-dimethylmethcathinone **5.**

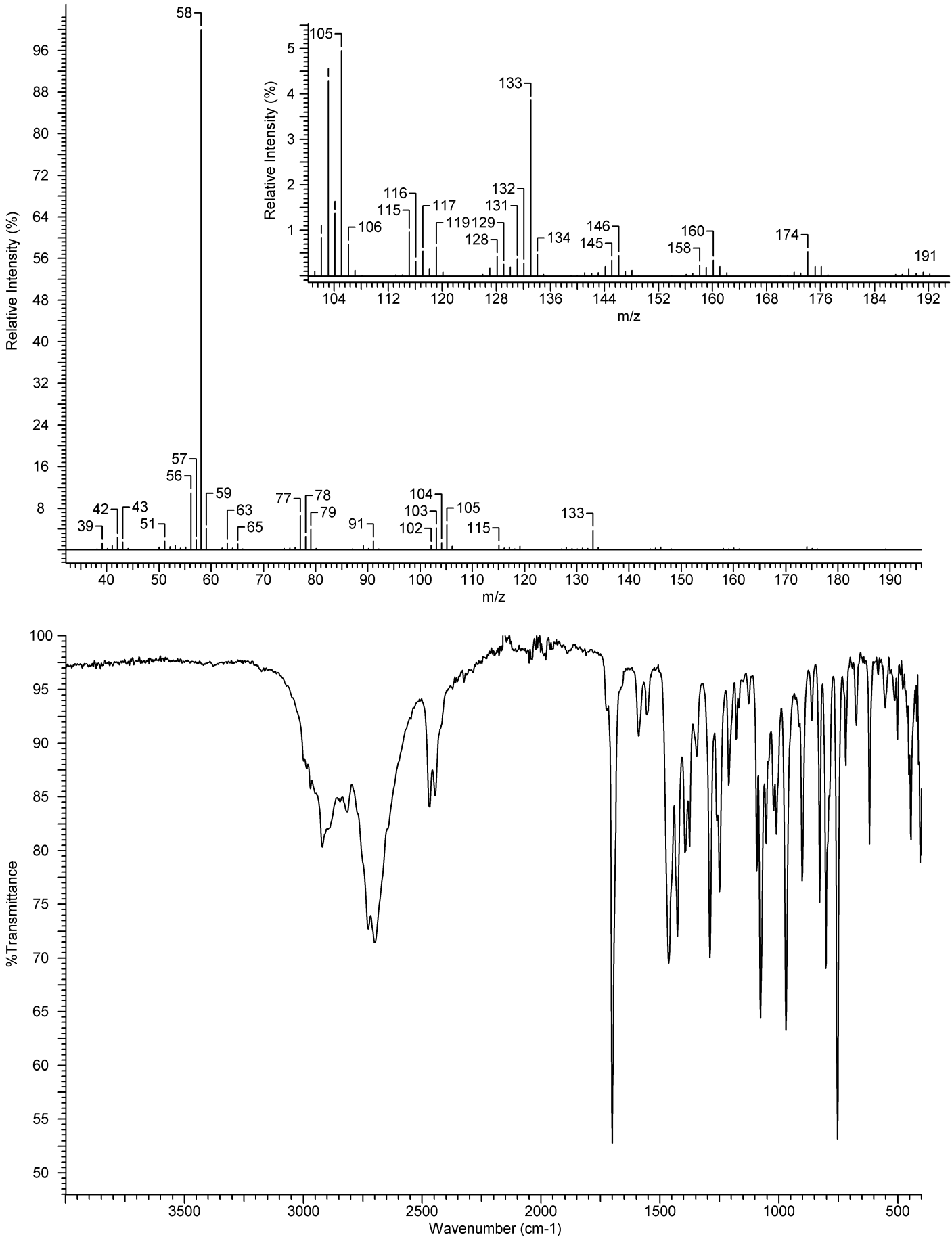

Figure 4 - Mass spectrum (upper) and of FTIR (lower) of 2,3-dimethylmethcathinone **6.**

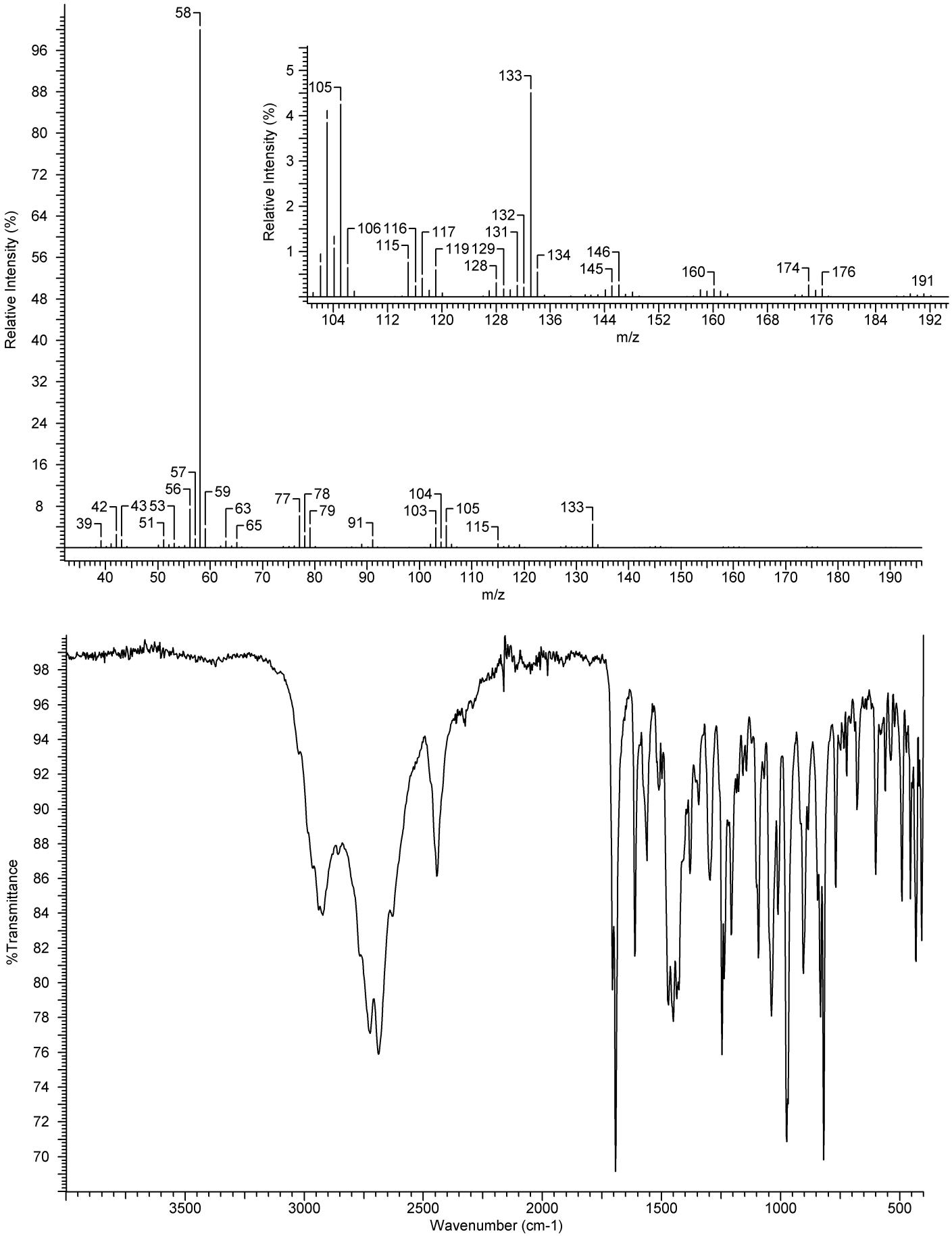

Figure 5 - Mass spectrum (upper) and of FTIR (lower) of 2,4-dimethylmethcathinone **7.**

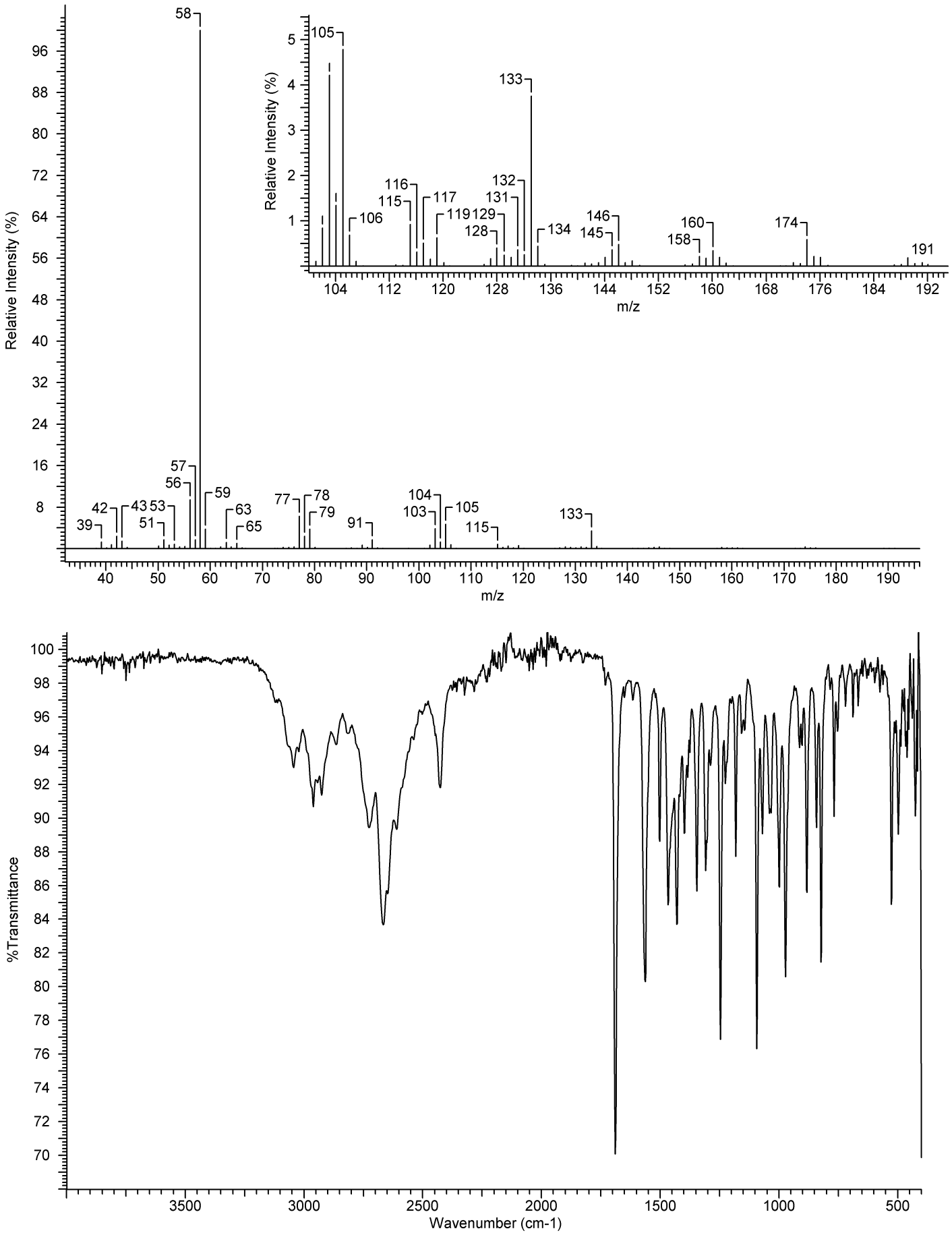

Figure 6 - Mass spectrum (upper) and of FTIR (lower) of 2,5-dimethylmethcathinone **8.**

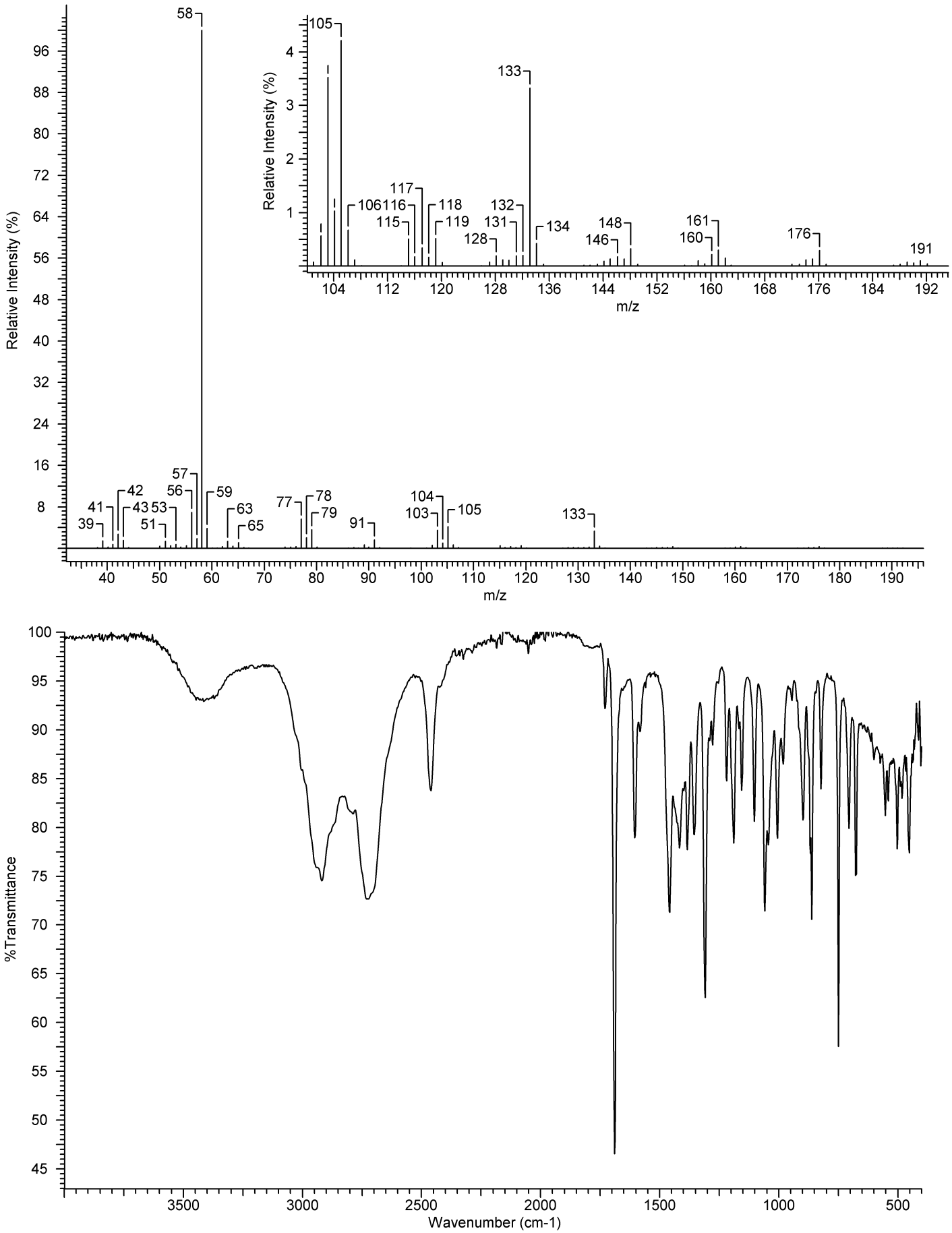

Figure 7 - Mass spectrum (upper) and of FTIR (lower) of 3,5-dimethylmethcathinone **9.**

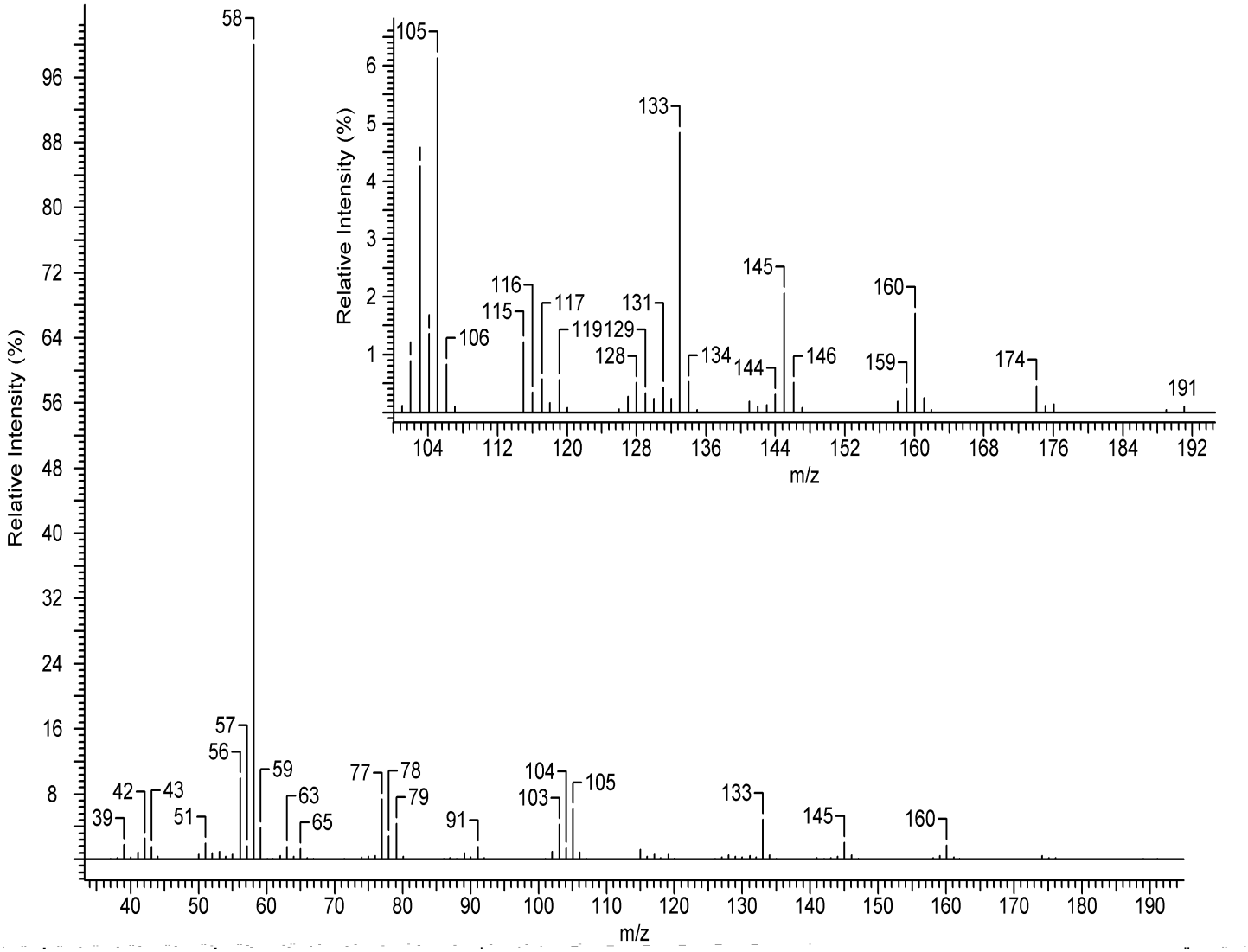

Figure 8 - Mass spectrum of suspected 2,6-dimethylmethcathinone **10.**

1.29 ppm). An NCH_3 is shown as a singlet (2.35-2.43 ppm) and the two benzene methyls are shown as one or two singlets (2.27-2.45 ppm). Benzene protons are found at 7.08-7.75 ppm and have varying multiplicities depending on where the methyl groups are located. The proton chemical shifts and peak patterns allow for fairly easy assignment of the two benzene methyl groups.

Symmetric benzene ring substitution (**9** and **10**) produce equivalent benzene methyls (proton and carbon). Compound **10** (not reported in this paper) is predicted to have a doublet (~8 Hz coupling) integrating to 2 hydrogens and a triplet integrating to 1 hydrogen, while **9** has two broad singlets (due to small spin-spin coupling constants) integrating to 2 and 1. Assymmetric benzene ring substitutions have different chemical shifts for the two benzene methyls, except for **5**, where they are nearly coincident. Compound **6** has 3 consecutive methines creating two doublets (at nearly the same chemical shift) and one triplet. Compound **7** has a broad doublet (H-5), a doublet (H-6), and a broad singlet for (H-3) with H-3 and H-5 having similar chemical shifts. Compound **5** has its benzene protons at distinctly different chemical shifts, with the following peak patterns: A small coupling doublet (H-2), a large coupling doublet (H-5), and a doublet of doublets (H-6). However, **5** has benzene methyl proton signals that are so close that they produce a broad singlet and their carbon signals, although different, are within 0.3 ppm.

Conclusions

3,4-Dimethylmethcathinone **5** is easily distinguished from its 5 positional isomers (**6**-**10**) via GC-MS. Each positional isomer produces a unique (although similar) mass spectrum. FTIR and NMR also delineates five of the possible six isomers (the 2,6-isomer **10** could not be synthesized in sufficient quantity for FTIR and NMR analysis).

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