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# Chemical analysis of two new designer drugs: buphedrone and pentedrone

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**The hydrochloride salts of buphedrone and pentedrone, two new designer drugs, have recently been identified in shipments destined for Canada. To confirm their identities, we have synthesized reference materials for these methcathinone analogues and herein provide complete characterization by FTIR, FT-Raman, $^1$H NMR, $^{13}$C NMR, GC/MS and ESI-HRMS. Copyright © 2011 John Wiley & Sons, Ltd.**

**Keywords:** buphedrone; pentedrone; methcathinone; designer drugs; synthetic cathinones

## Introduction

Since the 1990s, there has been a rapid explosion of new psychoactive substances,[1] including cathinone derivatives that have become popular in the early years of the twenty-first century. In 2010, we reported analytical data for methylone, bk-MBDB (butylone) and 4-methylmethcathinone (mephedrone), all of which had been found with increasing frequency in cross-border shipments by the Canada Border Services Agency (CBSA).[2] The CBSA has continued to intercept these substances and, in addition, has recently seized and identified two emerging designer drugs which have appeared in the international marketplace. Buphedrone **1** and pentedrone **2**, analogues of methcathinone **3**, were seized in Canada in 2011 in shipments from China (Figure 1).

In 1928, **1** and **2** and the corresponding amino alcohols were prepared to determine their effect on blood sugar.[3] As stated in a recent article, it has become 'clear that manufacturers of new substances (are) now trawling the world's scientific and patent literature in search of failed pharmaceuticals or, as they also became known, *designer medicines*'.[4] As part of this trend, **1** and **2** are now being manufactured to be sold (and used) for their psychoactive properties. This introduces an additional concern since there is little information on the pharmacology of these substances. These analogues are widely advertised for sale on the Internet and, while **2** does not appear to have been reported recently in the scientific literature, **1** has been detected in Japan[5] and also separately in a sample of ethcathinone in Ireland.[6]

The distribution of designer drugs over the Internet presents certain challenges. Several studies have discussed how the majority of products marketed as 'legal highs' on the Internet did not contain the claimed ingredients which were, instead, substituted with a controlled substance.[7,8] Designer drugs are often misdeclared or imprecisely declared to avoid detection or notice by law enforcement agencies and this was illustrated by our recent exhibits of **1** and **2**, which were declared as 'super absorbent polymer' and 'ZZ-1', respectively. The purity of the products purchased over the Internet is another issue where it has been shown that these products may contain additives or impurities, such as synthetic by-products and precursors.[6,9] In our seized exhibits of **1** and **2**, we observed approximately 2–8% of an impurity, tentatively identified as 1-(methylamino)-1-phenylbutan-2-one (*iso*-buphedrone) and 1-(methylamino)-1-phenylpentan-2-one (*iso*-pentedrone) respectively by gas chromatography-mass spectrometry (GC-MS) and nuclear magnetic resonance (NMR).

Most importantly for drug chemists, methcathinone analogues are controlled in many countries but, in general, cannot be unambiguously identified without certified reference standards or published peer-reviewed analytical data. Modifications to the chemical structure of a known psychoactive, such as **3**, can create a wide range of designer derivatives and certified reference standards are often unavailable when new substances are encountered. Therefore, the challenge for forensic laboratories is to find reliable analytical data, ideally from synthesized reference materials, to accurately identify new designer drugs.

To the best of our knowledge, complete characterization has not been published for **1** and **2**.[10] As a result, to confirm our identification of buphedrone and pentedrone, we have synthesized the hydrochloride salts of these racemic methcathinone analogues and provide complete spectroscopic (FTIR, FT-Raman, $^1$H NMR, $^{13}$C NMR) and spectrometric (GC/MS, ESI-HRMS) characterization.

## Experimental procedures

### Chemicals, reagents, and methods

All solvents and reagents were purchased from Sigma-Aldrich (Milwaukee, Wisconsin, United States), used without purification and were analytical grade. Derivatization grade *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) was used to prepare the trimethylsilyl derivatives for GC-MS. Trimethylsilyl derivatives were prepared by adding 5 mg of sample to 1 mL of 50% (*v/v*) MSTFA in chloroform and then heating to 70 °C for 1 h.

Sample solutions for analysis by NMR spectroscopy were prepared with 99.9% D anhydrous $CD_3OD$ from 1 mL ampoules.

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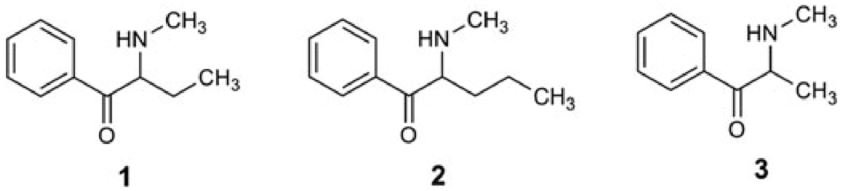
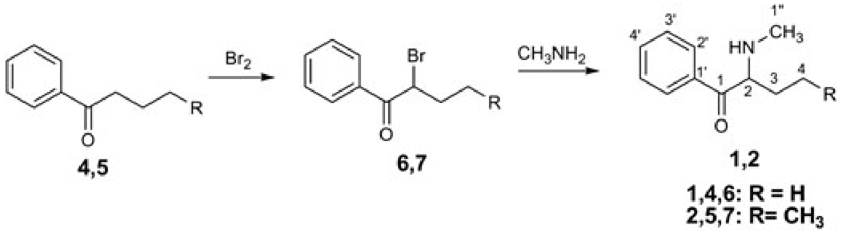


**Figure 1.** Chemical structures of buphedrone **1**, pentedrone **2** and methcathinone **3**.



**Scheme 1.** Synthetic pathway used to prepare **1** and **2**.

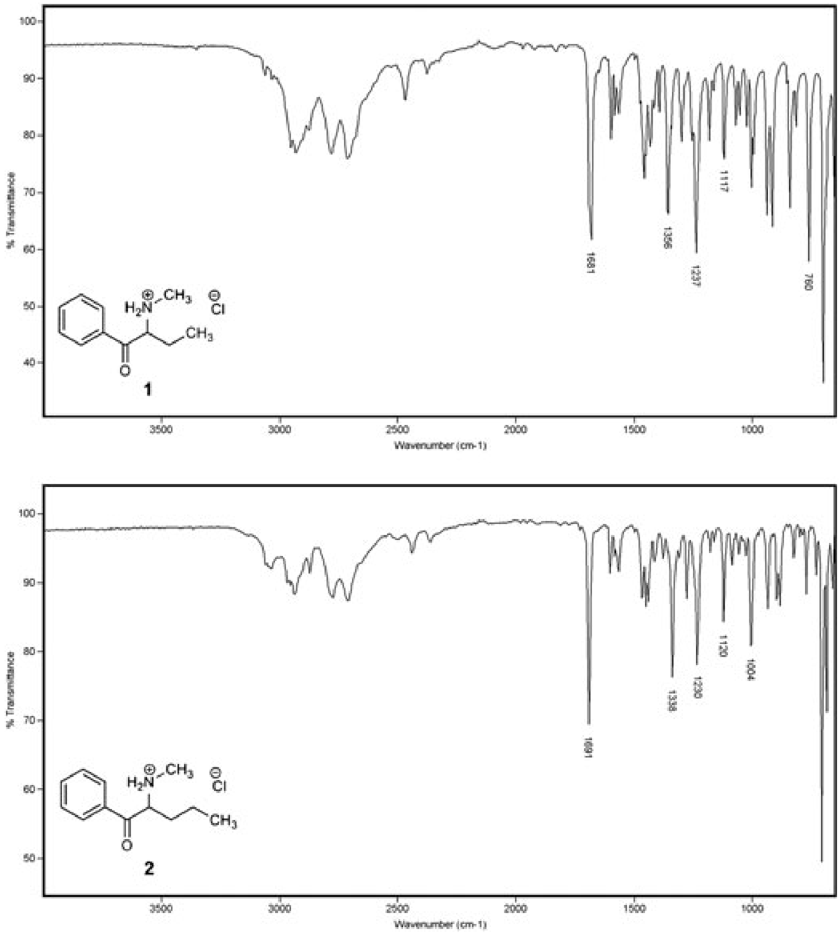


**Figure 2.** ATR-FTIR spectra of the hydrochloride salts of **1** (top) and **2** (bottom).

## Instrumentation

Attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectra were recorded on a Nicolet Avatar 370 FTIR, with single reflection diamond ATR accessory. Range: 4000–650 $cm^{-1}$, 16 scans and 4 $cm^{-1}$ resolution. Raman spectroscopy was performed using a Nicolet 6700 FTIR with NXR FT-Raman module on samples in an NMR tube with laser wattage at 1.0 W and an InGaAs detector. Range: 4000–100 $cm^{-1}$ Raman shift, 128 scans, 1064 nm Nd-YAG excitation laser.

GC-MS data was collected using an Agilent 7890A GC with autosampler 7693 series, 1 $\mu$L injection, split 150:1–4 mm single gooseneck liner (deactivated, with glass wool), DB5MS column (30 m × 0.25 mm × 0.25 $\mu$m) with constant flow (1 mL/min of helium) coupled to an Agilent 5975 C Mass Selective Detector. Electron ionization (EI) operating parameters were: inlet temperature 280 °C, interface temperature 280 °C, MS source 230 °C, MS Quad 150 °C, 70 eV ionization energy. The oven temperature program started at an initial temperature of 100 °C with a ramp of 10 °C/min to 300 °C. The final temperature was held for 25 min (total run time 45 min).

High-resolution mass spectra (HRMS) were obtained on a Thermo Scientific LTQ Orbitrap XL mass spectrometer by flow injection (with an eluent of 50:50 methanol/water with 0.1% formic acid) using electrospray ionization (ESI). The instrument was operated in positive mode with a resolution setting of 30 000 (FWHM) at *m/z* 400 and an internal lock mass of 413.26623 for the $[M+Na]^+$ ion for dioctyl phthalate. Data were acquired in full-scan mode over a range of *m/z* 100–1000 and all accurate mass measurements are within 1 part per million.

$^1H$ and $^{13}C$ NMR spectra were recorded in 5 mm NMR tubes on a Bruker AVANCE III 400 spectrometer at 400.13 MHz ($^1H$ NMR) or 100.62 MHz ($^{13}C$ NMR) on solutions in $CD_3OD$. Chemical shifts are given in parts per million (ppm) relative to the solvent signal of 3.31 ppm for $^1H$ NMR spectroscopy and 49.00 ppm for $^{13}C$ NMR spectroscopy. Coupling constants ($J$) are expressed in Hertz (Hz). The following abbreviations are used to designate NMR absorption patterns: s, singlet; d, doublet; t, triplet; app t, apparent triplet; q, quartet; m, multiplet.

## Synthetic procedures

The synthetic pathway used to prepare analogues **1** and **2** is given in Scheme 1. This synthetic route is commonly used for the synthesis of most cathinone analogues.[1] Reference materials were synthesized according to experimental conditions adopted from previous work.[2] Starting material butyrophenone **4** and valerophenone **5** were each treated with bromine to form the α-brominated precursor **6** and **7**, respectively, in quantitative yield. Methamination was achieved by reacting each of **6** and **7** with methylamine in tetrahydrofuran. After work-up, the hydrochloride salt for each analogue was prepared by adding a solution of ethereal hydrogen chloride to the corresponding α-methylamino derivative. The hydrochloride salts of **1** and **2** were each collected as white powders in high yields.

## NMR data for 1 and 2

### *Buphedrone **1** hydrochloride*

$^1H$ NMR ($CD_3OD$): δ 0.90 (3H, t, $J=7.5$ Hz, $CH_3$), 1.99-2.21 (2H, m, $CH_2$), 2.76 (3H, s, *N*-$CH_3$), 5.20 (1H, app t, CH), 7.61 (2H, m, H-3′,5′) 7.75 (1H, m, H-4′), 8.07 (2H, m, H-2′,6′). $^{13}C$ NMR ($CD_3OD$): δ 8.4 (C-4), 24.4 (C-3), 32.5 (*N*-$CH_3$), 65.4 (C-2), 129.9 (C-2′,C-6′), 130.4 (C-3′,C-5′), 135.1 (C-1′), 136.1 (C-4′), 196.6 (C-1). ESI-HRMS (*m/z*) calculated $[M+H]^+$: 178.1226; observed: 178.1225.

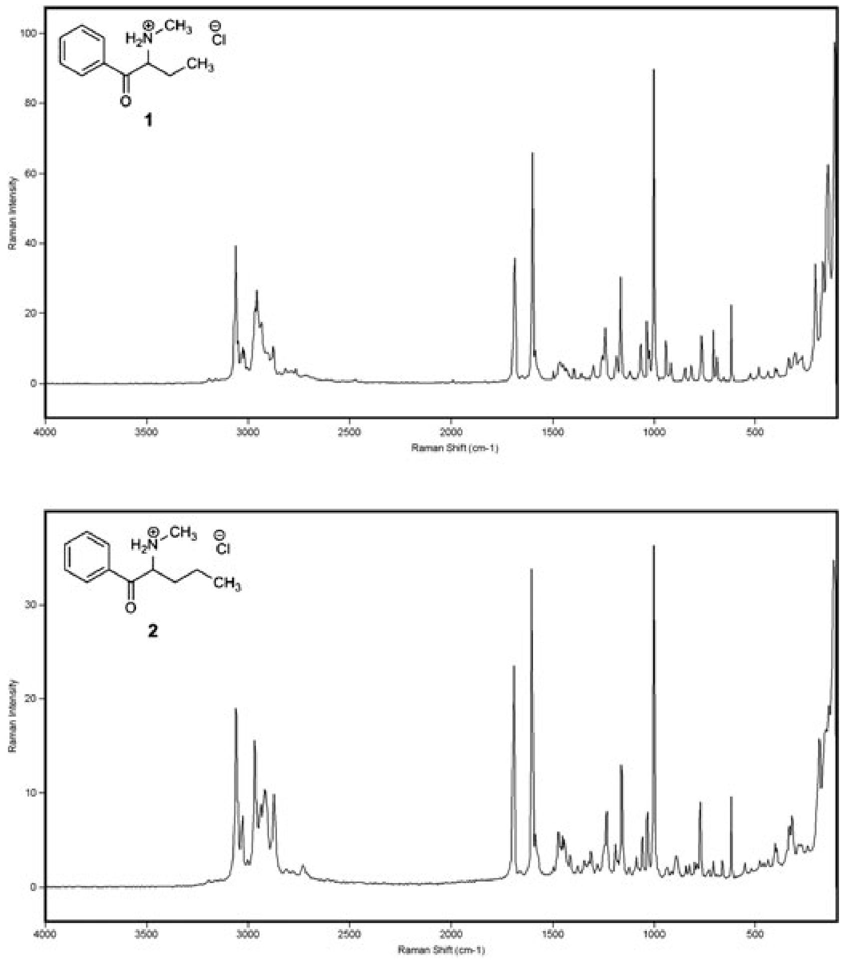


**Figure 3.** FT-Raman spectra of the hydrochloride salts of **1** (top) and **2** (bottom).

*Pentedrone **2** hydrochloride*

$^1$H NMR ($CD_3OD$): δ 0.89 (3H, t, $J = 7.3$ Hz, $CH_3$), 1.15-1.46 (2H, m, $C\underline{H}_2CH_3$), 1.90-2.07 (2H, m, $CHC\underline{H}_2$), 2.76 (3H, s, *N*-$CH_3$), 5.21 (1H, app t, CH), 7.61 (2H, m, H-3′,5′), 7.75 (1H, m, H-4′), 8.07 (2H, m, H-2′,6′). $^{13}$C NMR ($CD_3OD$): δ 14.1 (C-5), 18.5 (C-4), 32.6 (*N*-$CH_3$), 33.4 (C-3), 64.6 (C-2), 129.9 (C-2′,C-6′), 130.4 (C-3′,C-5′), 135.2 (C-1′), 136.1 (C-4′), 196.7 (C-1). ESI-HRMS (*m/z*) calculated $[M + H]^+$: 192.1383; observed: 192.1382.

## Results and discussion

### Vibrational Spectroscopy: Infrared and FT-Raman Spectra

The ATR-FTIR (Figure 2) and FT-Raman spectra (Figure 3) collected from samples of **1** hydrochloride and **2** hydrochloride synthesized in our laboratory were consistent with the IR and Raman spectra previously recorded for exhibits submitted from intercepted shipments.

The IR spectra for the hydrochloride salts of **1** and **2** display key features that help to classify these analogues as cathinones and exhibit unique band assignments that serve to distinguish between the two compounds. One important feature of cathinones is the conjugation of the carbonyl group with the phenyl group. The carbonyl stretching band absorbs at 1681 $cm^{-1}$ for **1** and 1691 $cm^{-1}$ for **2**. The broad pattern from about 3100 $cm^{-1}$ to 2200 $cm^{-1}$ in each analogue corresponds to a combination of C-H stretch (3100–2800 $cm^{-1}$) and absorption bands from the amine salt. For absorbances below 1500 $cm^{-1}$, the differences between **1** and **2** are more significant and allow for unambiguous identification.

IR and Raman spectroscopy are complementary techniques and, together, provide a more complete characterization of the molecule.

### Gas chromatography-mass spectrometry

The EI-MS are shown in Figure 4 for **1** and **2**. Molecular ions for underivatized methcathinone analogues are typically weak or absent. As a result, each analogue **1** and **2** was treated with MSTFA to give the thermally stable trimethylsilyl derivative for GC-MS analysis. The GC-MS data for the trimethylsilyl derivatives of **1** and **2** showed similar fragmentation patterns, giving molecular ions of *m/z* 249 and 263 respectively and characteristic α-cleavage (M-15) fragment ions at *m/z* 234 for **1** and *m/z* 248 for **2** (Figure 5). The molecular ions of the TMS-derivatives correspond to underivatized masses of 177 amu for **1** and 191 amu for **2**. The molecular mass for each analogue was confirmed through high resolution liquid chromatography-mass spectrometry (LC-MS).

The base peaks observed for silylated **1** and silylated **2** correspond to the formation of an iminium ion, which is also a feature observed in the fragmentation of methcathinone. For silylated **1**, the base peak of *m/z* 144 ($C_7H_{18}NSi^+$) is formed from α-cleavage of the benzylic bond. The same fragmentation is observed for silylated **2** and the base peak of *m/z* 158 ($C_8H_{20}NSi^+$) is expected from the extension of the alkyl chain. Both **1** and **2** showed an ion at *m/z* 105 due to the benzoyl cation, which subsequently forms a phenyl cation (after loss

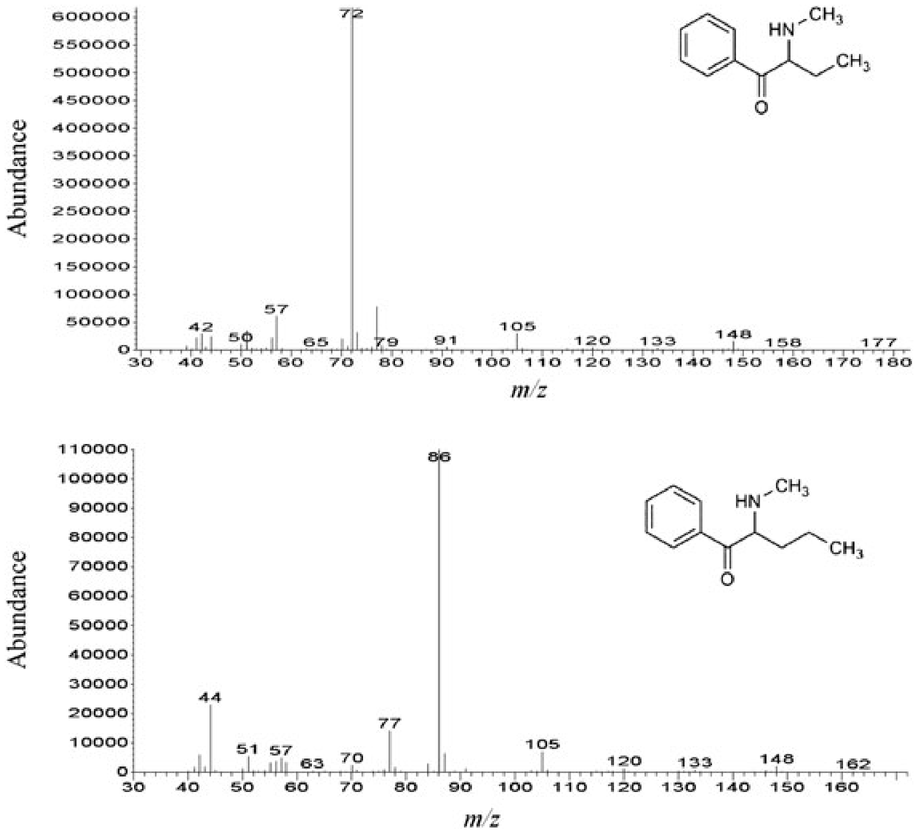


**Figure 4.** GC/MS data for **1** (top) and **2** (bottom).

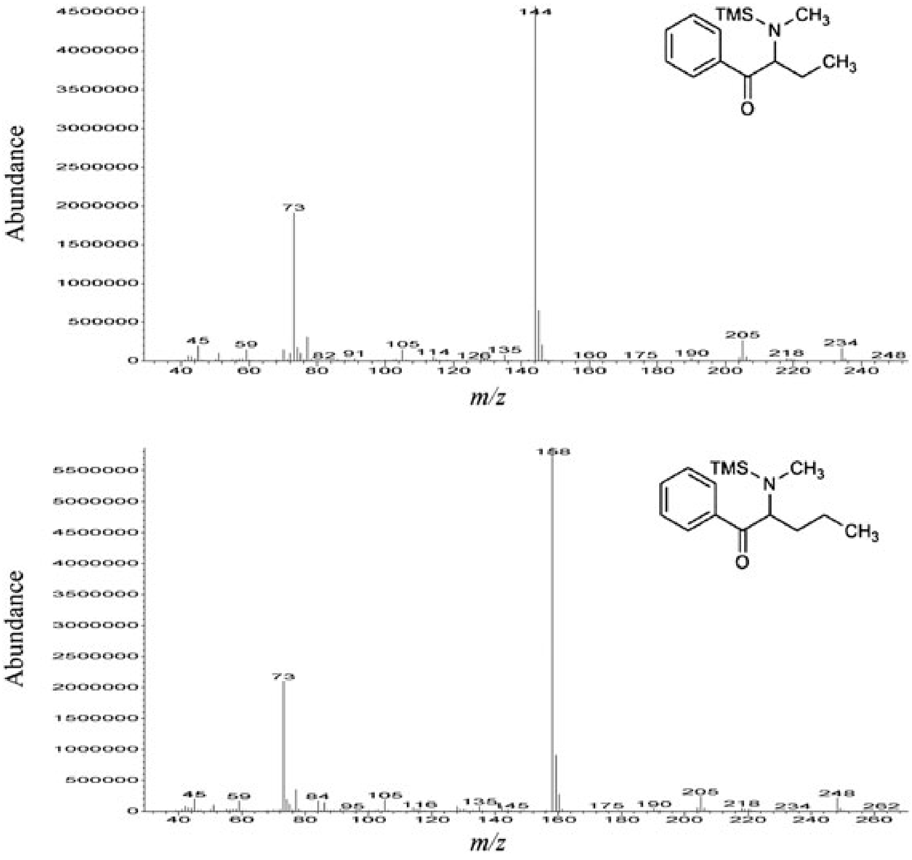


**Figure 5.** GC/MS data for the trimethylsilylated derivatives of **1** (top) and **2** (bottom).

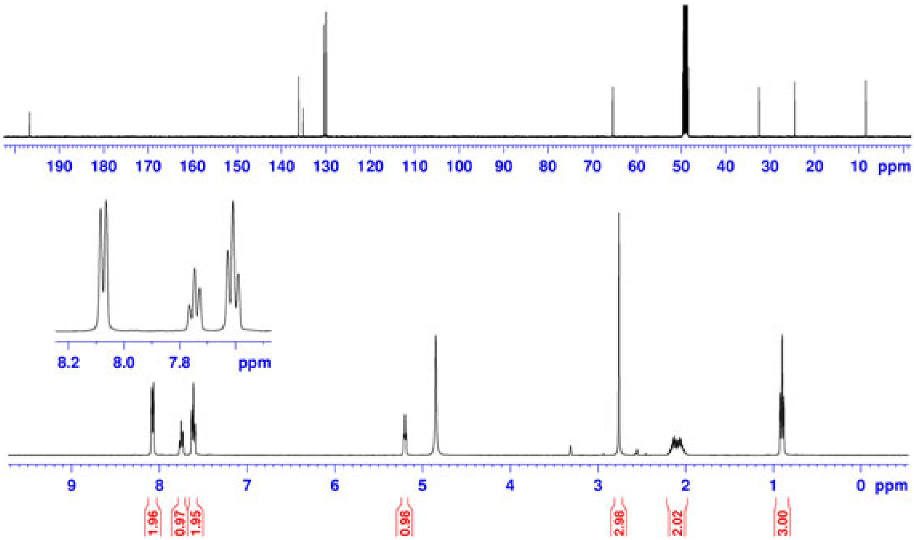


**Figure 6.** $^{1}H$ and $^{13}C$ NMR data for **1** hydrochloride in $CD_3OD$.

of CO) with *m/z* 77. Both silylated derivatives displayed a peak at *m/z* 73 for the trimethylsilyl ion.

## Nuclear magnetic resonance (NMR)

A combination of 1D ($^{1}H$, $^{13}C$, $^{13}C$-DEPT) and 2D (COSY, $^{1}H$,$^{13}C$-HSQC, $^{1}H$,$^{13}C$-HMBC) NMR experiments were used for structural elucidation. The $^{1}H$ and $^{13}C$ NMR spectra are presented in Figure 6 for **1** and Figure 7 for **2**. The two sets of spectra are similar in nature, although as expected, they each display characteristic differences.

In the $^{1}H$ NMR spectrum of **1** hydrochloride, the aromatic pattern and integration confirm the monosubstituted benzene ring. The aromatic protons were distinguished from one another by the integration and splitting, and the assignment was confirmed by the COSY experiment. Although the aromatic signals appear to be first order, they are slightly distorted from either second order effects or partially resolved long range coupling.

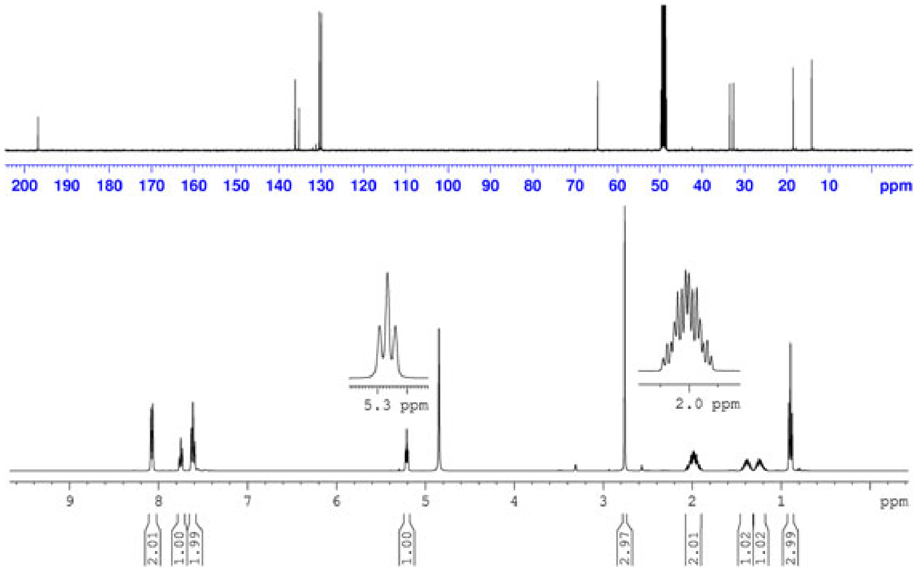


**Figure 7.** $^{1}H$ and $^{13}C$ NMR data for **2** hydrochloride in $CD_3OD$.

For this reason, the coupling constants could not be calculated and the signals are described as multiplets. The *N*-methyl moiety resonates as a large singlet (integration: 3H) at 2.76 ppm. The methinic proton H-2 (integration: 1H) is found at 5.20 ppm as an apparent triplet, therefore confirming the position of the *N*-methyl moiety on the alpha carbon of the butyrophenone skeleton and differentiating **1** from the *iso* equivalent recently reported in the analysis of some other substituted cathinones.[6] The proton at H-2 is coupled to non-equivalent methylene protons and, as a result, does not appear as a conventional first order triplet. In addition, this apparent triplet may appear slightly broadened due to unresolved longer range coupling. This type of broad signal was also observed in the corresponding methinic proton in 4′-methyl-α-pyrrolidinobutyrophenone (MPBP).[11] The alkyl side chain gives a multiplet centred at 2.11 ppm for the methylene protons H-3 and a triplet at 0.90 ppm for the terminal methyl group.

The $^{13}C$ NMR spectrum of **1** hydrochloride correlates with the $^{1}H$ NMR assignment. The carbon atoms were labelled in accordance with the $^{1}H$,$^{13}C$-HSQC and the data from $^{13}C$-DEPT experiments. The aromatic carbons C-2′/C-6′, C-3′/C-5′, C-1′ and C-4′ resonate at 129.9, 130.4, 135.1 and 136.1 ppm, respectively. C-1 gave a diagnostic carbonyl-carbon resonance at 196.6 ppm. The aliphatic side chain from the butyrophenone skeleton was assigned as followed: C-2 at 65.4 ppm, C-3 at 24.4 ppm and C-4 at 8.4 ppm. The carbon of the *N*-methyl group C-1″ is found at a chemical shift of 32.5 ppm.

The $^{1}H$ NMR spectrum for **2** hydrochloride was very similar to the $^{1}H$ NMR spectrum for **1** hydrochloride since the length of the alkyl chain is extended only by a methylene group in pentedrone. The methinic proton H-2 maintained a chemical shift of 5.21 ppm and the apparent triplet is more defined than that observed for **1**. The methylene protons H-3 appeared as a multiplet centred at 1.98 ppm and the two multiplets centred at 1.24 and 1.38 ppm correspond to the diastereotopic protons H-4. The data from the COSY experiment was used to distinguish methylene protons H-3 from H-4. The protons from the terminal methyl group H-5 remained relatively unchanged at 0.89 ppm.

Likewise, the $^{13}C$ NMR spectrum for **2** hydrochloride displayed similar aromatic, *N*-methyl, and carbonyl-carbon chemical shifts to **1** hydrochloride. The aliphatic side chain carbons C-2, C-3, C-4 and C-5 resonated at 64.6 ppm, 33.4 ppm, 18.5 ppm and 14.1 ppm, respectively.

## Conclusions

This work describes and provides analytical data for the designer drugs buphedrone and pentedrone to assist forensic chemists in their identification. These compounds have received little previous attention in the scientific literature. As a result, the hydrochloride salts of buphedrone and pentedrone were synthesized in our laboratory and their structures were characterized by ATR-FTIR, FT-Raman, NMR, GC-MS and ESI-HRMS.

The analytical data collected for the buphedrone hydrochloride and pentedrone hydrochloride synthesized in our laboratory was consistent with the corresponding data from samples intercepted previously by the Canada Border Services Agency.

### Acknowledgements

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