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TECHNICAL NOTE

CRIMINALISTICS

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Identification of 2-(ethylamino)-1-(4-methylphenyl)-1-pentanone (4-MEAP), a New "Legal High" Sold by an Internet Vendor as 4-Methyl Pentedrone*

ABSTRACT: Online vendors are offering a new legal high, 4-methylpentedrone (4-MPD). Information for potential users provided by internet vendors of 4-MPD includes incorrect structures and nonexistent CAS numbers. A sample of 4-MPD was obtained and analyzed using GC-MS, NMR, and LC-EIS. The fragmentation data from the GC-MS and LC-EIS produced an M-1 ion that suggested the molecular mass was 219 amu, rather than 205 amu as calculated for 4-methylpentedrone. The difference in molecular mass corresponded to the addition of a methyl group. Based on the mass and fragmentation pattern, two standards were synthesized, 2-(ethylamino)-1-(4-methylphenyl)-1-pentanone and 1-(4-methylphenyl)-2-(propylamino)-1-butanone. The synthesis involved bromination of the appropriate ketone followed by the reaction with ethylamine or propylamine. Based on the NMR data and unique fragmentation patterns produced by these molecules, the sample was identified as 2-(ethylamino)-1-(4-methylphenyl)-1-pentanone, not 4-methylpentedrone.

KEYWORDS: forensic science, 4-methylpentedrone, legal high, cathinone, analog, 2-(ethylamino)-1-(4-methylphenyl)-1-pentanone, 1-(4-methylphenyl)-2-(propylamino)-1-butanone, gas chromatography-mass spectroscopy, nuclear magnetic resonance

Legal highs are generally analogs of controlled substances that retain the psychoactive properties of the parent drug. In the United States, they are covered by the federal analogs when being sold or purchased for consumption. Consequently, vendors will advertise them as research chemicals, plant food, or even bath salts. A new legal high, 4-MPD, was been introduced by internet vendors of legal highs in the summer of 2013. According to internet drug forums and the vendors, 4-MPD is an abbreviation for 4-methylpentedrone. There are only a few user forum posts on 4-MPD. The effects are reported to be similar to, but milder than pentedrone. The primary motivation for use is that it is not controlled (1).

Based on the name, 4-methylpentedrone is an analog of the cathinone, pentedrone (Fig. 1). The 4-methylpentedrone is pentedrone with a methyl group at the para position on the phenyl ring for a molecular mass of 205 (Fig. 2).

A number of internet vendors that advertise 4-MPD also post a structure that corresponds to 2-(methylamino)-1-phenyl-1-butanone (buphedrone) with a para methyl group as shown in Fig. 3 (2,3) although the correct structure has been showing up more frequently (4–6). Others cite a Chemical Abstracts Service registry (CAS) number of 89669-27-9, which according to SciFinder (7), is not a valid number (8). Another listed the CAS number as 879669-95-1, the identifier for pentedrone, not 4-MPD (9). A final example of chemical misinformation provided by internet vendors is the display of the same structure for 4-MPD; Alpha-PVT, a thiophene analog of pentedrone; and 5f-AKB48, a cannabimimetic (10,11).

There is a CAS number for 4-methylpentedrone, 1373918-61-6. IUPAC name is 2-(methylamino)-1-(4-methylphenyl)-1-pentanone, and the formula is $C_{13}H_{19}NO$. There are no published references or commercial sources, and the properties listed are predicted (12).

A sample of 4-MPD was obtained as a free sample from an online vendor who offered research chemical in volumes as low as 0.500 g. The package had been shipped from China, and the products were labeled "face powder." Face powder is a legitimate product, generally a loose cosmetic powder (13).

The sample was analyzed and determined to be 2-(ethylamino)-1-(methylphenyl)-1-pentanone (4-MEAP). The CAS number for 4-MEAP Chloride salt is 18297-05-7 and a search of SciFinder (4) yields three references for patents, all from the late 1960s, early 1970s. The only commercial supplier is Cayman Chemical, who has recently added it as a forensic reference material (14). The CAS number for the base form is 746540-82-9 and a search yields no references and one supplier, FCH Group (15).

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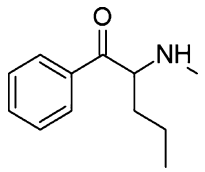


Fig. 1—*Pentedrone.*

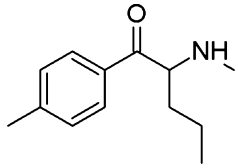


Fig. 2—*4-methylpentedrone, (4-MPD), MW = 205.*

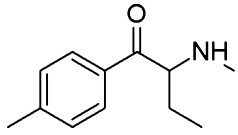


Fig. 3—*Structure of 4-methyl buphedrone.*

Materials & Methods

Reagents and Solvents

Dimethyl sulfoxide-d_6 was purchased from Cambridge Isotope Laboratories (Andover, MA, USA), and $CHCl_3$ was purchased from Fisher Scientific (Pittsbury, PA, USA). LCMS grade water, acetonitrile, and formic acid were obtained from Fisher Scientific (Dublin, Ireland). All reagents used for the syntheses of the cathinone derivatives were obtained from Sigma-Aldrich (Arklow, Ireland).

Product from Internet Vendors

One product, labeled 4-MPD, was received as a sample from an online vendor.

Gas Chromatography-Mass Spectrometry (GC/MS)

The vendor sample and standards were run on an Agilent 5973 mass selective detector (MSD; EI mode, 70 eV; m/z 40–450; source temp. 260°C) coupled to an Agilent 6890 GC (injector temperature 250°C; 1 μL injected in splitless mode; carrier gas, helium 1 mL/min, tuned with perfluorotributylamine (PFTBA)) fitted with a 30 m × 0.25 mm HP-5MS capillary column coated with 0.25 mm bonded 5% phenyl, 95% dimethylpolysiloxane (Agilent HP-5 ms Capillary GC Column, Agilent Technologies 19091S-433). The temperature program was as follows: initial temperature, 100°C, initial hold, 3.0 min; ramp rate, 20°C/min, temperature 140°C, hold 2.0 min; ramp rate, 5°C/min, temperature 150°C, hold 2.0 min; ramp rate, 5°C/min, temperature 160°C, hold 5.0 min; ramp rate, 20°C/min, final temperature, 250°C.

Liquid Chromatography/Electrospray Ionization Mass Spectrometry (LC-ESIMS)

LC-MS was performed on Agilent 1100 LC system (Böblingen, Germany) using an Allure PFP Propyl column (5 μm, 50 × 2.1 mm; Restek, Bellefonte, PA, USA): eluent A — acetonitrile containing 0.1% formic acid, eluent B — water containing 0.1% formic acid). The LC system was coupled to a Hewlett Packard/Agilent 1100 MSD (Santa Clara, CA, USA) using the following conditions: ESI mode (positive; TIC, m/z 50–600), capillary voltage 3000 V, drying gas (N_2) 12 L/min at 350°C, and nebulizer (N_2) pressure 60 psig. The mobile phase was 2% A (0–3 min.) followed by a linear gradient up to 60% A at 10 min and then up to 80% A at 15 min at a flow rate of 1000 μL/min. The system was allowed to equilibrate at 2% A for 5 min between runs. The fragmentor voltage for in-source CID was set at 70 V. The mass spectrometer was tuned according to the manufacturer's instructions using ESI Tuning Mix G2421A (Agilent Technologies). The retention times were 9.73 for 4-MEAP, 9.75 for the vendor sample, and 9.74 for 4-MPB.

Nuclear Magnetic Resonance (NMR) Spectroscopy

^1H (600 MHz) and ^{13}C (150 MHz) data were recorded on a Bruker AV600 NMR spectrometer using a 5 mm TCI cryoprobe and 16-32 scans. Approximately 5.0 mg of each sample was dissolved in 1 mL DMSO-d_6.

High-resolution Electrospray Mass Spectrometry — (ESI-HRMS)

High-resolution electrospray mass spectra were recorded on an LTQ Orbitrap Discovery (Thermo Fisher, Bremen, Germany). Compounds were analyzed by infusion (5 μL/min.). Full accurate high-resolution (30,000) mass scans (50–2000 Daltons) were performed in positive electrospray mode. The following conditions were used: drying gas — nitrogen (10 L/min); capillary temp., 310°C; spray voltage, 4 kV; capillary voltage, 22 V; and tube lens, 77 V.

Synthesis

The cathinone derivatives were synthesized as previously described (16). This involved bromination of the appropriate ketone followed by the reaction of the resulting α-bromo ketone with a solution of ethylamine or n-propylamine in tetrahydrofuran and conversion to their hydrochloride salts using a solution of hydrogen chloride in diethyl ether.

2-(ethylamino)-1-(4-methylphenyl)-1-pentanone (4-MEAP)

^1H NMR (d_6 DMSO) δ 8.00 (d, J = 8 Hz, 2 H, H-2/6), 7.42 (d, J = 8 Hz, 2 H, H-3/5), 5.24 (m, 1 H, H-2′), 3.01 and 2.88 (2 × m, 2 H, H-1″), 2.41 (s, 3 H, H-6′) 1.94 and 1.88 (2 × m, 2 H, H-3′), 1.32 and 1.08 (2 × m, 2 H, H-4′), 1.27 (t, J = 7 Hz, H-2″) and 0.77 (t, J = 7 Hz, 3 H, H-5′); ^{13}C NMR (d_6 DMSO) δ 196.1 (C-1′), 145.8 (C-1), 132.0 (C-4), 130.0 (C3/5), 129.2 (C-2/6), 60.6 (C-2′), 41.4 (C-1″), 32.2 (C-3′), 21.6 (C-6′), 17.5 (C-4′), 14.0 (C-5′) and 11.4 (C-2″).

1-(4-methylphenyl)-2-(propylamino)-1-butanone (4-MPB)

^1H NMR (d_6 DMSO) δ 8.00 (d, J = 8 Hz, 2 H, H-2/6), 7.41 (d, J = 8 Hz, 2 H, H-3/5), 5.24 (m, 1 H, H-2′), 2.91 and 2.76 (2 × m, 2 H, H-1″), 2.41 (s, 3 H, H-6′) 2.08 and 1.96 (2 × m, 2 H, H-3′), 1.75 (m, 2 H, H-2″), 0.89 (t, J = 7 Hz, H-2″) and 0.77 (t, J = 7 Hz, 3 H, H-5′); ^{13}C NMR (d_6 DMSO) δ 195.9 (C-1′), 145.8 (C-1), 132.0 (C-4), 130.0 (C-3/5), 129.2 (C/2/6), 61.8 (C-2′), 47.9 (C-1″), 23.3 (C-3′), 21.6 (C-6′), 19.3 (C-2″), 11.33 (C-3″) and 8.8 (C-4′).

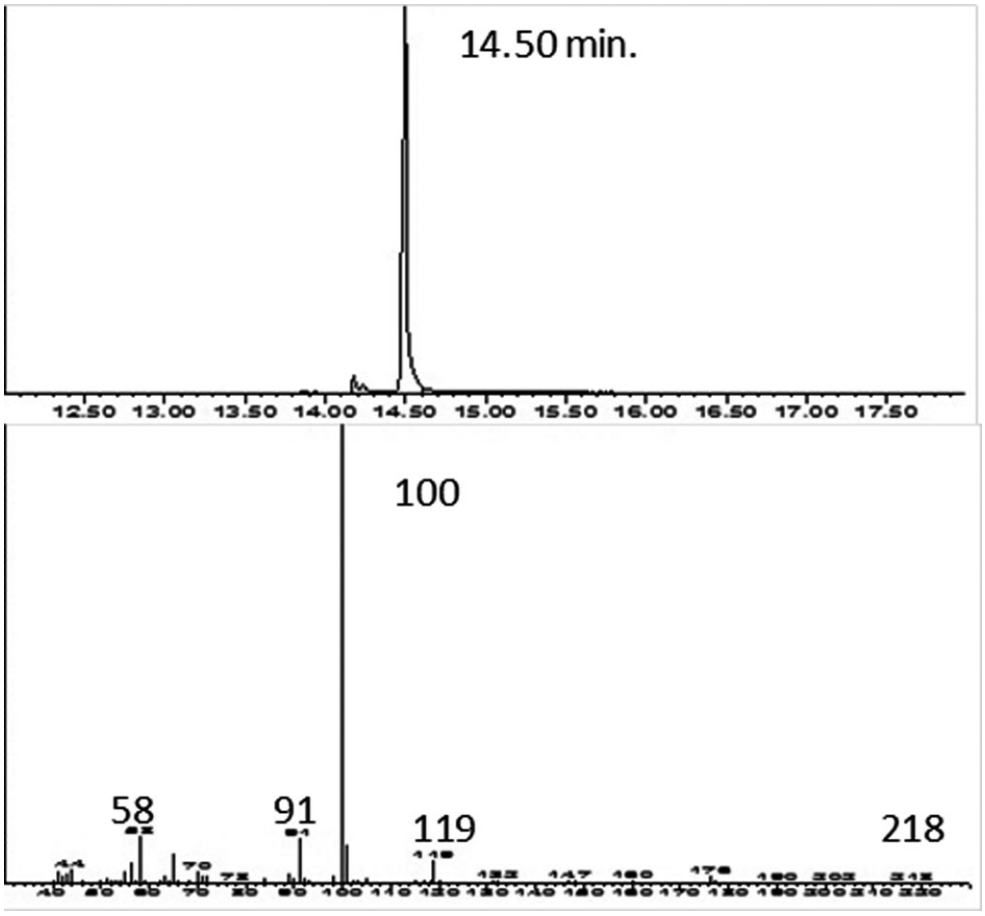


Fig. 4—*GC-MS of vendor sample.*

Results and Discussion

The initial GC-MS and LC-ESI of the vendor sample are not consistent with the mass or fragmentation pattern predicted for 4-methylpentedrone (Fig. 4). The most abundant ions are m/z 100, 58, 91, and 119. A signal at m/z 41 is present, but at very low abundance. The highest m/z was 218. The molecular mass for 4-MPD is 205 amu, so neither the parent ion nor the M-1 is evident. The peak at 218 (M-1) indicates that the vendor sample labeled 4-MPD structure might contain an additional CH_2. Two small impurity peaks were also eliminated as possible 4-MPD and were not further identified.

Fragmentation of 4-methylpentedrone at the carbonyl would result in m/z of 119 and 86. A fragment with m/z of 119 is present in the MS of the vendor sample, but not one at m/z 86. The base peak at m/z 100 indicates a methylene group inserted into an alkyl chain rather than attached to the benzyl side of the molecule. Interpretation of the GC-MS data resulted in a possible formula of $C_{14}H_{21}NO$.

The formula was confirmed with ESI-HRMS, which produced a molecular mass of 220.1698 and an [M+H]+1 isotope peak with an abundance of 16% for the unknown. Using values from the NIST Atomic Weights and Isotopic Compositions (17), the exact mass for the protonated molecule was calculated to be 220.17013 amu.

The abundance of the [M+H]+1 was calculated to be 16%, using the values of 1.1, 0.38, and 0.20 for C, N, and O, respectively. The difference between the calculated and measured molecular mass is 0.0003 amu, within the accepted error of 0.0015 amu or 1.5 mmu.

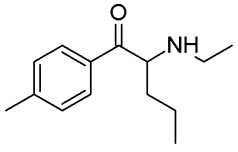


Fig. 5—*2-(ethylamino)-1-(4-methylphenyl)pentan-1-one (4-MEAP), MW = 219.*

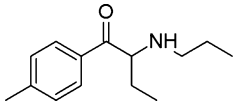


Fig. 6—*1-(4-methylphenyl)-2-(propylamino)butan-1-one (4-MPB), MW = 219.*

Two isomers with the formula $C_{14}H_{21}NO$ that could produce the GC-MS obtained for the vendor sample were 2-(ethylamino)-1-(4-methylphenyl)-1-pentanone (4-MEAP) and 1-(4-methylphenyl)-2-(propylamino)-1-butanone (4-MPB) in Figs 5 and 6, respectively. These were synthesized and characterized by GC-MS, NMR, and FTIR-ATR. The 2- and 3-methyl substituted isomers were not considered at this time.

The retention time for 4-MEAP is 14.49 min, and the three most abundant peaks are m/z 100, 91, 58, and 119. As with the

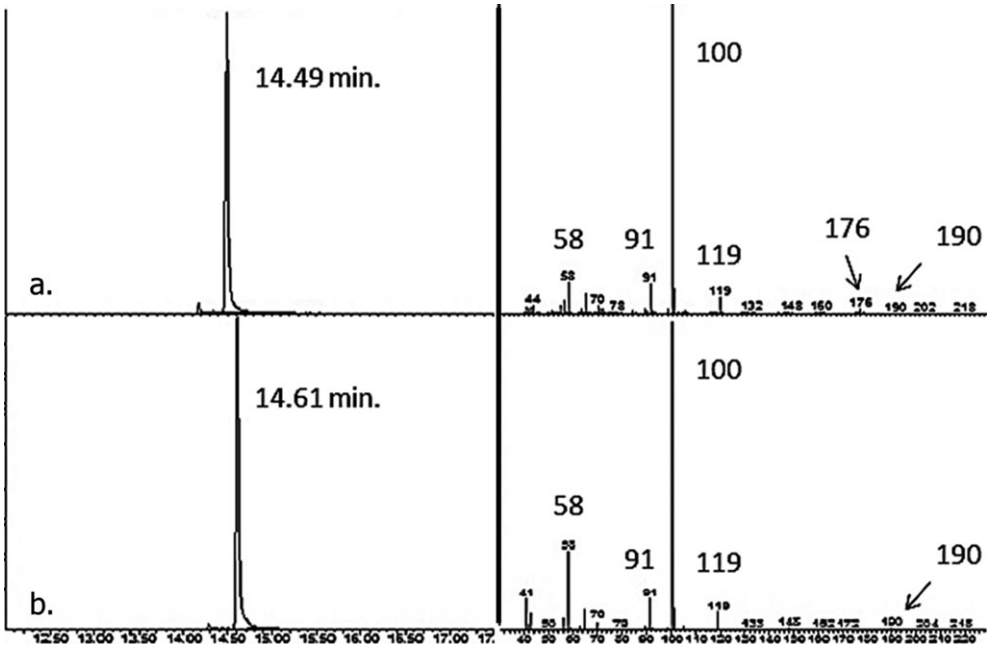


Fig. 7—*GC-MS of a. 4-MEAP and b. 4-MPB.*

vendor sample, the parent ion is not present, but the M-1 ion at m/z of 218 is evident at low abundance (Fig. 7). The ESI-HRMS produced an M+H of 220.1696.

The retention time for 4-MPB is 14.61 min and the three most abundant ions are m/z 100, 58, 91, and 41. Again, there is a small peak at m/z 218 for the M-1 ion and the ESI-HRMS produced an M+H of 220.1694 (Fig. 7).

In addition to the difference in retention times, the two isomers can also be distinguished by their mass spectra as unique fragmentation patterns were obtained for both. For 4-MEAP, fragmentation at the carbons alpha to the nitrogen result in loss of methyl and propyl fragments resulting in fragments at m/z 204 and 176, respectively. Fragmentation of 4-MPB at the N alpha carbons would both result in ethyl groups, m/z 29, with a corresponding ion at m/z 190. While the MS for 4-MEAP contains a small peak for m/z = 190, the 4-MPB does not contain a peak at m/z 176. The sample labeled 4-MPD matches both the retention time and MS for 4-MEAP.a.

In Fig. 8, the ^{1}H, ^{13}C and, ^{13}C DEPT NMR spectra for 4-MEAP, the vendor sample and 4-MPB have been stacked to aid in comparison. The spectra for the sample and 4-MEAP are nearly identical, with the ppm shift values differing by <0.2 ppm, if at all.

The NMR data for the standards are summarized in Tables 1 and 2 for ease of comparison. The carbon positions that are specific to an isomer are in bold italics. The positions that are in equivalent locations, but different environments are in italics. In 4-MEAP, the two terminal CH_3′s are in different environments and are separated by 0.5 ppm. The methylene in the ethylamino group is distinct from the skeletal methylenes. In 4-MPB, the

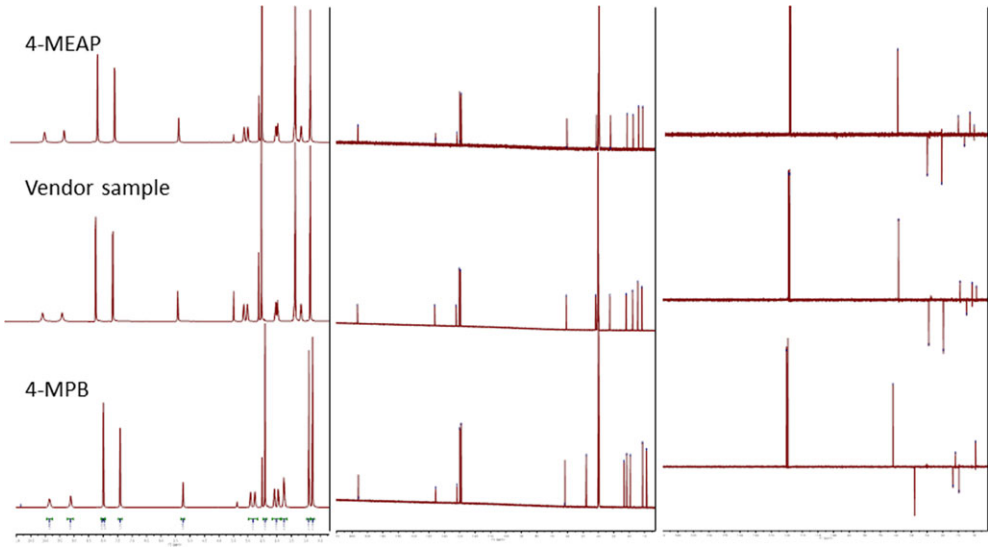
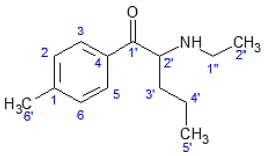


Fig. 8—*The ^{1}H (left) ^{13}C (center) and DEPT ^{13}C NMR spectra (left) for the vendor sample, 4-MEAP, and 4-MPB.*

TABLE 1—*Summary of NMR spectroscopic data for 4-MEAP and the vendor sample. Note that carbons 2 and 6, and 3 and 5 are equivalent.*

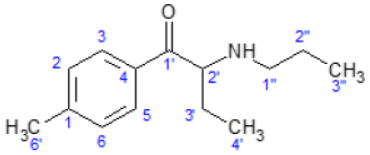
Position	Carbon/ppm	DEPT/ppm, phase/+/−	Proton/ppm
1	145.8 (145.8)	–	–
2,6	129.2 (129.1)	129.3 + (129.3)	8.0
3,5	130.0 (130.0)	130.2 + (130.2)	7.4
4	132.0 (132.0)	–	–
1′	196.1 (196.1)	–	–
2′	60.72 (60.55)	60.72 + (60.72)	5.25
*3′**	*32.20 (32.20)*	*32.36 − (32.36)*	*1.85*
4′	*17.52 (17.52)*	*17.68 − (17.68)*	*1.15*
5′†	***13.99 (13.99)***	***13.99 (13.99)***	***0.75***
6′	21.59 (21.59)	21.75 + (21.59)	2.35
1″	*41.31 (41.43)*	*41.59 − (41.59)*	*3.0*
2″	*11.41 (11.41)*	*11.41 (11.41)*	*1.25*



*Values in parentheses are for the vendor sample.
†Rows in grey and italics indicate atoms in equivalent positions in each isomer, but in a different chemical environment.
‡Rows in dark grey with bold text indicate an atom specific to an isomer.

TABLE 2—*Summary of NMR spectroscopic data for 4-MEAP. Again, carbons 2 and 6, and 3 and 5 are equivalent.*

Position	Carbon/ppm	DEPT/ppm (phase)	Proton/ppm
1	145.79	–	–
2,6	129.17	129.35 (positive)	8.0
3,5	130.00	130.17 (positive)	7.4
4	132.0	–	–
1′	195.85	–	–
2′	61.86	61.92 (positive)	5.25
*3′**	*23.29*	*23.45 (negative)*	*2.0*
4′	*8.79*	*8.94 (positive)*	*0.5*
6′	21.58	21.75 (positive)	2.35
1″	*47.86*	*47.93 (negative)*	*2.75*
2″	*19.31*	*19.49 (negative)*	*1.5*
3″†	***11.32***	ppm not assigned	***0.75***



*Rows in Grey indicate atoms in equivalent positions in each isomer, but in a different chemical environment.
†Rows in dark grey with bold text indicate an atom specific to an isomer.

two alkyl chains are quite similar, with the skeletal chain being further downfield than the alkyl chain.

Conclusions

A free sample of a new legal high, 4-MPD, was offered by an internet vendor in the summer of 2013. A user searching the internet for information about this legal high would have found more misinformation about 4-MPD than factual. In recent searches, internet vendors of 4-MPD have replaced the structure of 4-methyl buphedrone with that of 4-MEAP, although 4-methylpentedrone is still listed as the common name. The substance shipped as a free sample is 2-(ethylamino)-1-(4-methylphenyl)-1-pentanone (4-MEAP), not 4-methylpentedrone as claimed. The crystal structure for 4-MEAP was obtained on June 18, 2014 and is available as supplemental material through the Journal of Forensic Sciences Web site. The results of these experiments further illustrate the cocktail of inadequately researched chemicals being offered as psychoactive drugs by internet vendors (18).

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1. Asymmetric unit of TCD61. Displacement ellipsoids shown at 50%. Hydrogen atoms omitted for clarity.

Figure S2. Packing diagram of TCD61 viewed down the a axis. Dashed lines indicate the strong stair-step hydrogen bonding between the amino group hydrogen atoms and the chloride ion.