FACT SHEET

4-methylamphetamine (4-MA)

April 2012

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A. General information

Recent collected/biological samples in Belgium

Substance: 4-methylamphetamine  
Date of seizure: March 2012  
Date of analysis: April 2012  
Product type: powder  
Color: Yellow/brown  
Region: Antwerpen/Aalst

Updated  
April 2012

Type  
Psychotropic substances

Group  
Phenethylamines

Name  
4-MA (4-methylamphetamine)

Nature of substance  
4-Methylamphetamine is a stimulant derivative of amphetamine, that was investigated in the past as an appetite suppressant and has serotonin, norepinephrine, and dopamine releasing properties (see PIHKAL, under 2,5-DMA, #54).

Other names  
4-MA; PAL-313; Aptrol

B. Alerts

Alerts

Belgium, April 2012  
A recent death in Antwerp was reported to the Belgian Early Warning System on Drugs (BEWSD) by prof. dr. H. Neels (ZNA Stuivenberg), linked to the consumption of 4-methylamphetamine. A yellow/white powder was found in the pockets of the patient, containing amphetamine and 4-methylamphetamine. During the previous 24 hours, the patient had also used ketamine and cocaine. The patient died following extreme hyperthermia and cardiac arrest, and could not be resuscitated.

A second death was reported by Chemiphar NV in the region of Aalst (ASZ Aalst). Post-mortem bodily fluids contained amphetamine and 4-methylamphetamine. Also, a powder was found containing amphetamine, caffeine, 4-methylamphetamine and diphenylisopropylamine.
Belgium, 7 October 2011
Six recent cases involving 4-methylamphetamine have been reported to the Belgian Early Warning System on Drugs.
In total it concerns 3 fatalities and 3 intoxications.
1. 1 fatality + 1 intoxication; august 2011, Lommel (two friends)
   - Fatality: blood: 1200ng/mL 4-methylamphetamine; 715 ng/mL amphetamine and traces of cannabis
   - Intoxication: serum: 120 ng/ml 4-methylamphetamine, no amphetamine, sildenafil
2. Intoxication; September 2011, Antwerpen
   Urine screening positive for amphetamine, confirmation by GC/NPD and –MS also revealed presence of 4-methylamphetamine
3. Fatality, September 2011, parket Dendermonde
   - Blood: 1450 ng/mL 4-methylamphetamine; 750 ng/mL amphetamine; olanzapine
   - Powder sample: identification of 4-methylamphetamine, amphetamine and caffeine
4. Fatality, August 2011, parket Oudenaarde, Zottegem
   - Blood: 1980 ng/mL 4-methylamphetamine; 1070 ng/mL amphetamine, 2.4 ng/ml THC; 230ng/ml MDMA.
   - Powder sample: 14% amphetamine-SO4; 56% 4-methylamphetamine; 13% caffeine
5. Intoxication, August 2011, parket Oudenaarde, Herzele
   - Suicide attempt by overdose
   - Patient thought to have bought ‘Special K’ (Ketamine)
   - Powder sample: 16% amphetamine-SO4; 64% 4-methylamphetamine; 15% caffeine.

UK, 10 October 2011
2 fatalities reported by Simon Elliott at ROAR Forensics:
October 2010: 33 yr old male – sent home from work with flu-like symptoms. 4-Methylamphetamine in the blood (3.49 mg/L), amphetamine (16.5 mg/L) and cannabis. No other drugs or alcohol detected. [Only recently confirmed].
May 2011: 22 yr old male – taken Ecstasy night before, snorted cocaine/”MCat”. Agitated, hot, shaking. 4-Methylamphetamine in the blood (3.77 mg/L), unidentified cathinones and ethanol (27 mg/dL blood). No other drugs detected.

Reports to EMCDDA

Switzerland: On 2 March 2012 the NFP reported a seizure of 7,28g yellow powder seized on 16/12/2009 by the SKL (Swedish police) at Växjö.

Not country-specific or non-EU country (Europol Other): On 11 November 2011 Europol reported the “Summary of request related to national information on 4-methylamphetamine”.

Not country-specific or non-EU country: 13 October 2011, Switzerland:
Informed that the Youth Outreach Street Work, Zurich have analysed last year in September a Speed sample containing Amphetamine and 4-Methylamphetamine.

Poland: On 17 October 2011 the NFP reported a seizure of 4 samples of powder 2g each, 2x light yellow, 2 x light pink, total weight of seizure unknown seized on 06/10/2011 by the Police at Szczecin. Containing 83-86% amphetamine-SO4; small amount of 4-methylamphetamine and DPIA.
Hungary: On 25 March 2011 the NFP reported a seizure of 21g yellow powder and 1768g yellow powder containing also amphetamine, seized in October 2010 by the Police at Keszthely.

Denmark: On 22 December 2010 the NFP reported 1 seizure of 1g white powder seized by Slagelse Police on 15/12/2010.

Germany: In December 2010, the German FP reported a seizure of 938 gr of 4-MA white powder, seized in 14.07.2010. The FP also informed that '4-MA was presumably seized hidden in amphetamine samples four times in Germany in 2010. 4-Methylamphetamine could not be identified with certainty but its by-products point directly to 4-Methylamphetamine.'

Croatia: On 17 November 2010 the NFP reported 3 seizures of light yellow powder seized by the Police in June, September and October

France: On 22 July 2010, the French NFP informed on a sample containing 4-MA collected by SINTES on 17 June 2009 in Grenoble, and analysed by the French Customs (SCL-laboratoire de Paris)

Norway: In February 2010 the NFP reported a seizure of 120 tablets seized by the Norwegian customs at Oslo in December 2009. Kripos (the National Criminal Investigation Service) analysed this product labeled "Green Stinger" and sold in the US as a "dietary supplement". According to the label it contains "Ephedra extract" along with other ingredients. The analysis revealed that no ephedrine was present. Instead the MS-data indicated a mix of several compounds: 1-phenylethylamine, 2-phenylethylamine, beta-methyl-phenethylamine, N,N-dimethyl-phenethylamine, 4-methylamphetamine, N-benzyl-1-phenylethylamine as well as caffeine and yohimbine.

Belgium: On 14 December 2009 the NFP reported a seizure of 16 bags, each containing a piece of yellow paste in aluminium foil. 9 bags contained about 5g of paste, 1 bag 39g, 6 bags 70 to 80g. It was seized at Flanders in October by the local police services. 4-methylfenylaceton was also detected. Also other by-products were found that indicate that a Leuckart-reaction was used.

C. Pictures
D. Clinical information

Usage
**Subjective effects in man:**
Information from user forums on the Internet suggest that it may have entactogenic effects in addition to stimulant properties. However, reports vary in the extent and type of effects experienced. The effects are said to last 2-4 hours. Based on in vitro and in vivo studies in animals it is probable that it is has less reinforcing and stimulant effects as compared to amphetamine and it only partially substitutes for this in rats trained to discriminate (Higgs and Glennon, 1990). It is relatively non-selective for the dopamine, noradrenaline and serotonin transporters, compared with amphetamine which doesn’t have great affinity for SERT. Increased serotonin activity is associated with decreased reinforcing abilities (Wee et al, 2005). It has been proposed to be used for treatment of psycho-stimulant abuse since it lacks behavioural stimulant effects in monkeys (Kimmel et al, 2011).

**Dose:**
Doses of 75 mg are reported to produce adrenergic stimulation; at twice this dosage signs of mild toxicity such as salivation, coughing and vomiting are expected (PIHKAL).
Activity on drug user forums suggest that it can be insufflated or taken orally.

**Health risks**
There have been reports of five fatalities and three intoxications in Belgium, where 4-methylamphetamine was present (3 in August/September 2011, and two more fatalities in March 2012). Two fatalities in which 4-methylamphetamine was implicated were also recently confirmed in the UK. There is also a case in the literature from 1989 of a man admitted to hospital with sympathomimetic effects. When treated with a beta blocker, the effects worsened. After discharge he reported experiencing disabling feelings of anxiety for several weeks. A sample of the purported substance he inhaled was identified to contain p-methylamphetamine and N, p-dimethylamphetamine (Bal et al., 1989).

E. Legal status

**Croatia: controlled**
In February 2011 new Amendments to the List of drugs, psychotropic substances, plants used to produce drugs and substances that can be used in the production of drugs (precursors) (OG 19/11) were adopted by the Minister of Health. In the document psychoactive substances were put under legal control.

**Denmark: controlled**
Since May 2011 has been added to the list of controlled substances

**United Kingdom: controlled**
F. References

Wellman P. J. et al., Changes in feeding and locomotion induced by amphetamine analogs in rats, Drug and Alcohol Dependence 100 (2009) 234–239

Kimmel H. L. et al., Behavioral and neurochemical effects of amphetamine analogs that release monoamines in the squirrel monkey, Pharmacology, Biochemistry and Behavior 94 (2009) 278–284


G. Chemistry

Systematic chemical name
1-(4-methylphenyl)propan-2-amine

Chemistry
Other chemical names and variants
4-methylamphetamine, 4-MA

Chemical Abstracts Service (CAS) registry number
22683-78-9

Molecular information
Molecular structure:

![Molecular structure diagram]

Molecular formula: \( \text{C}_{10}\text{H}_{15}\text{N} \)

Molecular weight: 149.23

Identification and analytical profile can be found at the end of this document. Analytical spectra were kindly provided by the University of Antwerp, Belgium.
+ESI Product Ion (0.183 min) Frag=80.0V CID@5.0 (150.1 -> ***) 4MA-40ng-pos-CE5.d

**Fragmenter:**
80V

**Optimal CE:**
133.1: 5V
105.1: 15V

**Precursor:**
150.2 (pos)
Identification of 4-Methylamphetamine in a seized Amphetamine Mixture

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Key words: 4-methylamphetamine, structure elucidation, NMR, GC-MS

Abstract

In 2010 a new designer drug 4-methylamphetamine was detected in an amphetamine mixture. The structure was elucidated by GC-MS after electron ionization (EI) and chemical ionization (CI) with methane as reagent gas, product ion spectrometry (EI-MS/MS with argon as collision gas under normalized conditions) of the immonium ion, and by NMR spectroscopy. Additionally, the acetyl, the trifluoroacetyl, the heptafluorobutyryl, and the formyl derivatives of 4-methylamphetamine have been prepared and measured on GC-MS.

1. Introduction

In 2010 a new designer drug was detected in an amphetamine mixture. The seized mixture of an off-white powder contained besides amphetamine, caffeine, di-(phenylisopropyl)amine (DPIA) and some by-products an other amphetamine type compound 1 (Fig. 1).

Fig. 1. GC-MS total ion chromatogram (TIC) of the alkaline diethyl ether extract [1].

Searching of the EI-MS-spectrum of 1 against the mass spectral library Designer Drugs [2] revealed 4-methylamphetamine as first hit. However, not all isomers were present in the library and no retention index was given. So, further measurements for structure elucidation had to be done.
2. Material and Methods

2.1. GC-MS analysis

For GC-MS analysis an alkaline diethyl ether extract was prepared. GC-MS spectra were recorded on a Finnigan TSQ 7000 triple stage quadrupole mass spectrometer coupled to a Thermo gas chromatograph (fused silica capillary column DB1, 30 m x 0.25 mm, film thickness 0.25 µm). The temperature program used consisted of an initial temperature of 80 °C (1 min) followed by a ramp to 280 °C at 15 °C/min finally held for 15 min. The carrier gas was helium (constant flow 1 ml/min). The ion source temperature was 150 °C, the electron ionization energy was 70 eV with an emission current of 400 µA. The scan time was 1s, and the scan range was m/z = 30 - 600. The spectrum after chemical ionization (CI) was recorded with methane as reagent gas under the same conditions. The scan range was m/z = 50 - 600 for the CI-MS spectrum. Product ion spectra were recorded with argon as collision gas in EI mode and normalization of the collision conditions with n-butylbenzene [3]. For derivatization the alkaline diethyl ether extract was divided into several portions, evaporated at room temperature under a gentle nitrogen stream and derivatized with methyl iodide, acetic acid anhydride, N-methyl-N-trimethylsilyl trifluoroacetamide (MSTFA), trifluoroacetic acid anhydride, heptafluorobutyric acid anhydride, and formyl chloride in a sealed glass vial at 70 °C for 30 min. Derivates were reconstituted in diethyl ether or chloroform for GC-MS measurement.

2.2. NMR analysis

NMR spectra were recorded with a Bruker Avance spectrometer operating at resonance frequencies of 500 MHz for ¹H-NMR-spectra. The mixture of compounds was previously separated on a preparative Waters LC-MS system, using a Waters Xbridge C18 column (5.0 µm, 19 mm x 150 mm) and a water/acetonitrile gradient. The eluents consisted of A (water + 0.05% formic acid) and B (acetonitrile). The gradient was as follows: initial A:B = 95:5 lineary to 25:75 in 10 min, then 0:100 until 14 min. The eluate was fractionated and collected. After evaporation some mg of the unknown compound were isolated. About 1 mg of the compound was dissolved in 500 µL perdeuterated water containing sodium acetate (1.9 ppm) as a quantitative standard (no quantification done). The following NMR-spectra were recorded using standard pulse programs at 300 K to obtain resonance frequencies of all proton- and carbon-atoms: one-dimensional (1D) ¹H-NMR, 2D-gradient selected ¹H,¹H-COSY, ¹H,¹3C-HSQC and -HMBC. ¹H,¹3C-HSQC and -HMBC correlate geminal and vicinal protons, carbon atoms with their directly attached protons, and carbon and proton atoms generally separated by three or two bonds, respectively. All spectra were referenced to TSP (trimethylsilyl propionic acid sodium salt).

3. Results and Discussion

Compound 1 was identified as 4-methylamphetamine (para-methylamphetamine). GC-MS after chemical ionization (CI) with methane as reagent gas revealed a molecular weight of 149 amu showing strong losses of 17 amu from the fragments m/z = 150 ([M+H]+), 178 ([M+29]+), and 190 ([M+41]+) indicating a primary amine (Fig. 2). The mass spectrum after electron ionization (EI) was not identical with the isobaric cathinone and showed as base peak signal the fragment m/z = 44 (member of the immonium ion series) and minor fragments at m/z = 65, 77, 91, 105, 117, and 134 shifted by 14 amu in comparison to amphetamine indicating a methyl substitution in the aromatic moiety (Fig. 3).
The structure of the amino moiety was elucidated by product ion spectrometry (EI-MS/MS with argon as collision gas under normalized conditions) of the immonium ion m/z = 44 to be a N-unsubstituted immonium ion with an alpha-methyl-substituted carbon atom (Fig. 4, I + II). The second possible structure of the immonium (Fig. 4, III) is clearly ruled out by its different product ion spectrum [4,5]. The results of the GC-MS elucidation for compound 1 were consistent with an amphetamine bearing a methyl group in the aromatic moiety.
Fig. 4. Product ion spectrum of the immonium ion m/z = 44 of compound 1 (I) and corresponding data base [4] entries (II and III).
To clear the position of the methyl group NMR spectroscopic measurements were necessary. Before NMR measurement compound 1 was isolated from the mixture by preparative LC/MS. NMR measurements in deuterated water showed clearly a para substitution pattern (two doublets at 7.22 ppm and 7.27 ppm in $^1$H-NMR, Fig. 5) with the corresponding $^{13}$C-signals at 132.3 and 132.5 ppm, respectively. The additional methyl group in the aromatic ring resonated at 2.34 ppm as a singlet in the $^1$H-spectrum with a chemical shift of 22.9 ppm for the corresponding $^{13}$C-signal (see HSQC-spectrum in Fig. 7). The assignment of the quarternary carbon atoms was done by a Hetero-Multiple-Bond-Correlation (HMBC, not shown). Chemical shifts for all atoms are shown in Fig. 6.

Fig. 5. $^1$H-NMR spectrum of 4-methylamphetamine after purification, S = standard (sodium acetate), I = Impurity.

Chemical shifts of compound 1:

<table>
<thead>
<tr>
<th>Atom</th>
<th>$\delta$ [ppm]</th>
<th>Atom</th>
<th>$\delta$ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-2/2'</td>
<td>7.22 (d, $^3J_{2,3} = 7.8$ Hz)</td>
<td>C-1</td>
<td>136.0</td>
</tr>
<tr>
<td>H-3/3'</td>
<td>7.27 (d, $^3J_{3,2} = 7.8$ Hz)</td>
<td>C-2</td>
<td>132.3</td>
</tr>
<tr>
<td>H-5</td>
<td>2.34 (s)</td>
<td>C-3</td>
<td>132.5</td>
</tr>
<tr>
<td>H-6</td>
<td>2.91 (d, $^3J_{6,7} = 7.2$ Hz)</td>
<td>C-4</td>
<td>140.4</td>
</tr>
<tr>
<td>H-7</td>
<td>3.61 (tq, $^3J_{7,6} = 7.2$ Hz, $^3J_{7,8} = 6.6$ Hz)</td>
<td>C-5</td>
<td>22.9</td>
</tr>
<tr>
<td>H-8</td>
<td>1.30 (d, $^3J_{8,7} = 6.6$ Hz)</td>
<td>C-6</td>
<td>42.5</td>
</tr>
</tbody>
</table>

4-Methylamphetamine

Fig. 6. NMR results of compound 1.
Fig. 7. Aromatic and aliphatic region of the HSQC-spectrum of 4-methylamphetamine.

Besides the dimer of amphetamine (di-(phenylisopropyl)amine, DPIA) which is built as a common by-product during amphetamine synthesis, the dimer of 4-methylamphetamine and even the mixed dimer of amphetamine and 4-methylamphetamine was detected (Fig. 8) indicating the synthesis of amphetamine and 4-methylamphetamine in the same batch. Because of the existence of two chiral centres in the molecules diasteromers of each dimer can be detected.

Fig. 8. Synthesis side products of 4-methylamphetamine (continued on next page).
Fig. 8 (continued). Synthesis side products of 4-methylamphetamine.
Additionally, the formyl, the acetyl, the trifluoroacetyl, the heptafluorobutyryl, the trimethylsilyl and the methylated (p-methylmethamphetamine!) derivatives of 4-methylamphetamine have been prepared and measured on GC-MS (Fig. 9).

Fig. 9. Derivatives of 4-methylamphetamine.
Fig. 9 (continued). Derivatives of 4-methylamphetamine.
4. Conclusion and Outlook

In a seized amphetamine mixture besides amphetamine, caffeine, and di-(phenylisopropyl)-amine (DPIA) the new designer drug 4-methylamphetamine and some of its synthesis by-products were detected. The structure of 4-methylamphetamine was elucidated by GC-MS, GC-MS/MS and NMR. Some derivatives have been prepared and their EI-GC-MS spectra were recorded. Meanwhile 4-methylamphetamine has been seized by various police organizations in Germany [6] and was already detected in serum samples of drivers in Germany [7].

5. References

[1] Structure formulas and mass spectra were generated and processed by Chemograph Plus Software, P. Rösner, DigiLab Software GmbH, www.chemograph.de.


[4] Junge Th, Rösner P, Westphal F. Product ion mass spectra of important organic ions, a free printed version can be ordered from the authors.

