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Impurity Profiling of Amphetamine and Methamphetamine Using Gas Chromatography Mass Spectrometry (GCMS) Harmonised Methods (Pemprofilan Bendasing Amfetamin dan Metamfetamin Menggunakan Kaedah Pengharmonian Analisis Kromatografi Gas Spektrometri (GCMS))

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ABSTRACT

Impurity profiling of drug seizures is a scientific approach employed to understand drug trafficking networks thus has becoming increasingly important in criminal investigation. This paper presents the feasibility of using the Collaborative Harmonisation of Methods for the Profiling of AmphetamineType Stimulants (CHAMP) established by the European Commission authority for impurity profiling of amphetamine and methamphetamine samples. Both drugs were analysed using similar extraction procedure and analytical conditions. The impurities were extracted from an alkaline buffer solution (pH8.1) using toluene prior to gas chromatography-mass spectrometry (GC-MS) analyses. The results showed that the reproducibility of the method for detecting amphetamine and methamphetamine ranged between 7.4-8.9 and 6.2-8.4 %RSD, respectively. Identification of impurities was performed by referencing against the available MS databases as well as to previous reported impurity profiling studies. Phenyl-2-propanone (P2P), also known as benzyl-methylketone (BMK), as well as other specific impurities such as 4-methyl-5-phenylpyrimidine, bis-(1-phenylisopropyl) amine, N-formylamphetamine and N,N-di (b-phenylisopropyl) amines were identified in the amphetamine samples, indicating Leuckart's pathway as the route of synthesis. Because P2P was also detected in the methamphetamine samples, the possible route of synthesis of the methamphetamine samples being Leuckart's, nitrostyrene synthesis or reductive amination could not be ruled out.

Keywords: Amphetamine; chromatographic profiles; impurities; mass spectrum; methamphetamine

ABSTRAK

Pemprofilan bendasing bagi rampasan dadah merupakan pendekatan saintifik yang diguna pakai bagi memahami jaringan penyeludupan dadah yang menjadi semakin penting dalam penyiasatan jenayah. Kertas ini membentangkan kebolehlaksanaan Kaedah Pengharmonian Kolaboratif untuk Pemprofilan Amfetamin (CHAMP) yang diwujudkan oleh Suruhanjaya Eropah bagi pemprofilan dadah amfetamin dan metamfetamin. Sampel telah dianalisa dengan melalui proses pengeksktrakan dan analisis yang sama. Pengeksktrakan bendasing dilakukan menggunakan larutan penimbal beralkali (pH8.1) dengan toluen sebelum analisis kromatografi gas-spektrometri (GC-MS) dijalankan. Kebolehulangan pengesanan yang direkodkan bagi amfetamin dan metamfetamin masing-masing ialah 7.4-8.9 dan 6.2-8.4% RSD. Pengenalpastian bendasing telah dilakukan dengan merujuk kepada pengkalan data MS dan kajian yang telah dijalankan sebelum ini. Fenil-2-propanon (P2P) atau juga dikenali sebagai benzil-metil-ke-ton (BMK) telah dikenal pasti dalam sampel amfetamin selain bendasing seperti 4-metil-5-fenilpirimidina, bis-(1-fenilisopropil) amina, N-formilamfetamina dan N, N-di (b-isopropil) amina yang menunjukkan penggunaan kaedah sintesis Leuckart. P2P telah dikesan di dalam sampel metamfetamin yang menunjukkan laluan sintesis bagi dadah ini adalah berkemungkinan Leuckart, nitrostirena atau reduktif aminasi.

Kata kunci: Amfetamin; bendasing; metamfetamin; pemprofilan kromatografi; spektrum jisim

INTRODUCTION

The abuse of synthetic drugs such as amphetamine and amphetamine type stimulants (ATS) has been a major social concern worldwide (United Nations Office on Drugs and Crime (UNODC) 2014). Being classified as ATS, amphetamine and methamphetamine are referred to as synthetic or designer drugs with well established illicit markets and increasingly popular as abusive agents (Isa et al. 2013; United Nations Office on Drugs and Crime (UNODC) 2014). It has been indicated that synthetic drugs seizures have increased globally within the last seven

years with the East and South East Asia regions recorded the highest number of people treated for synthetic drug addictions, in agreement with the prevailing trend in the national data obtained from the Royal Malaysia Police (RMP) records (Hamdan et al. 2015; United Nations Office on Drugs and Crime (UNODC) 2014). In comparison to the plant based drugs (e.g. heroin, opium & cocaine), synthetic drugs are relatively easy to manufacture using common household chemicals and solvents readily available from commercial sources such as hardware outlets and pharmacies (Abdullah et al. 2014; Baharudin et al. 2013).

Moreover, methods of production for such drugs are readily accessible from bogus sites over the internet (Cole 2003).

Amphetamine (street name *pil kuda* in Malaysia) and one of its analogous, the methamphetamine (street name *syabu* in Malaysia), share similar chemical properties i.e. having a basic amine group linked to a benzene ring, hence grouped together as phenethylamine substances (Figure 1).

The predominant routes for synthesising amphetamine are the Leuckart's reductive amination and nitrostyrene

(2 steps reaction), involving the use of P2P or BMK as the precursor (Figure 2). Other rarely encountered means of amphetamine production includes using norephedrine or norpseudoephedrine precursor (Abdullah et al. 2014; Allan & Ely 2011; Allen & Cantrell 1989; Stojanovska et al. 2013). On the other hand, methamphetamine is predominantly synthesised using eight synthetic routes, depending on the type of precursor available at hand. Commonly, either P2P or ephedrine/pseudoephedrine is used as the precursor (Figure 3). Since every synthetic

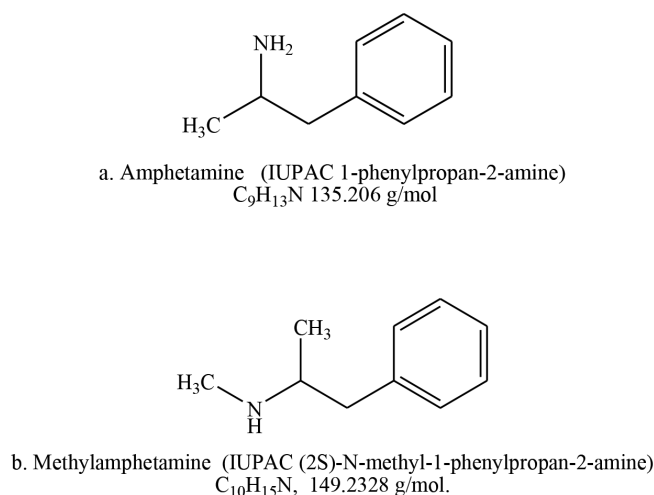


FIGURE 1. Chemical structures of amphetamine (a) and methamphetamine (b)

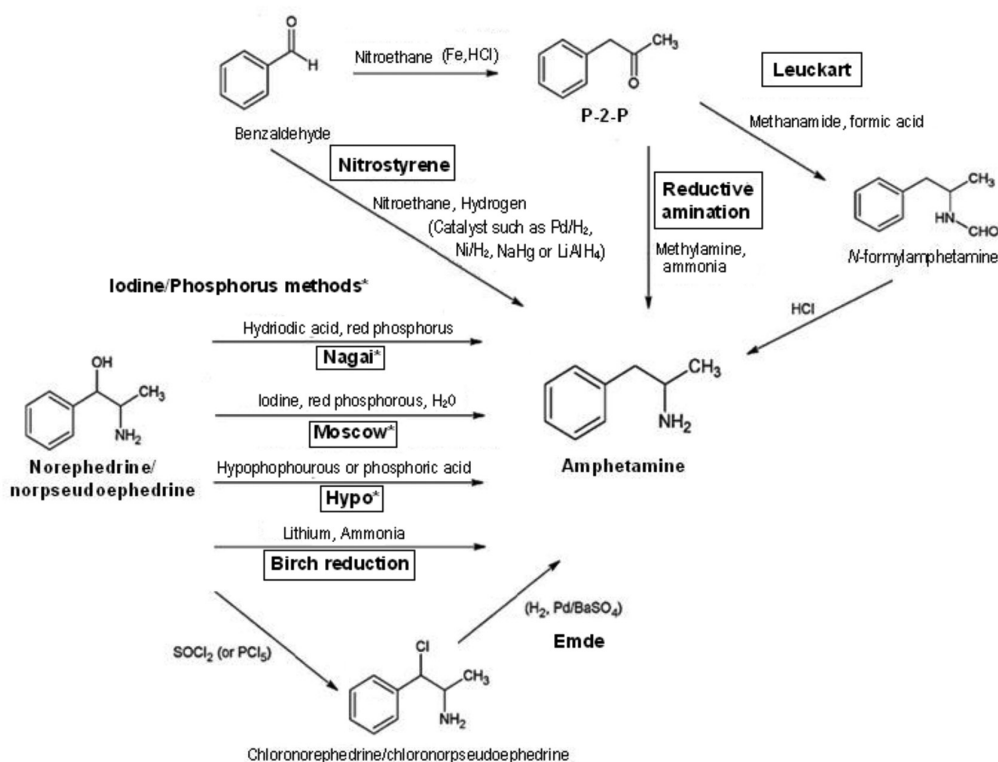


FIGURE 2. Simplified diagrammatic representation of various synthetic routes for clandestine amphetamine synthesis (Allen & Cantrell 1989; Stojanovska et al. 2013)

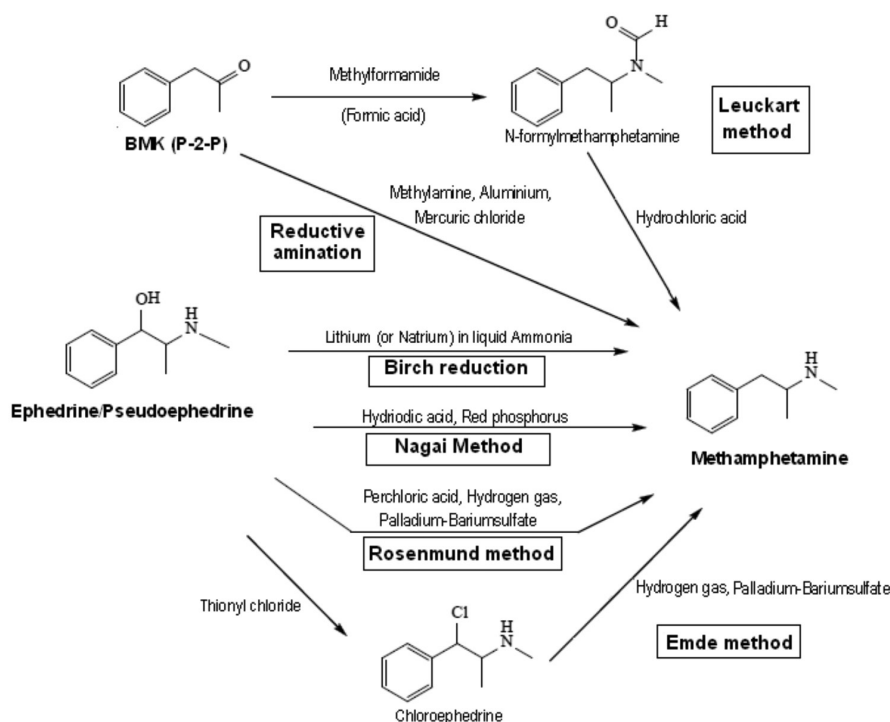


FIGURE 3. Simplified diagrammatic representation of various synthetic routes for clandestine methamphetamine synthesis (Hamdan et al. 2015; Kunalan et al. 2009)

route produces the intended final product as well as impurities and by-products, profile of impurities and by-products may be useful in advocating the type of precursor used and hence the synthetic route (Abdullah et al. 2014; Allan & Ely 2011; Allen & Cantrell 1989; Stojanovska et al. 2013).

In forensic illicit drug analysis, chromatographic profiling of the drugs following extraction procedure is usually performed to obtain information about impurities in drug samples. Impurities in illicit drugs arise from reactants, by products and also intermediate contaminants which give complicated chromatographic profiles that may be useful for profiling purposes. Due to the minute abundance of these impurities, forensic drug profiling focuses on identification of impurities peaks rather than quantification of the compounds as detection and identification of target impurities are adequate to suggest possible route of synthesis. Chromatographic profiles of the organic impurities from amphetamine and methamphetamines drug seizures have been proven to offer valuable information that is useful for characterisation as well as comparing and identifying the similarities and/or differences among illicit drug seizures (Abdullah et al. 2014; Power et al. 2014; Stojanovska et al. 2013; United Nations Office on Drugs and Crime (UNODC) 2014). In addition, extensive analysis of organic and inorganic compounds in drug profiling may establish the possible link or relationship between seizures; identify the origin or source of drug supply, drug trafficking route and distribution pattern as well as possible synthesis methods (Allan & Ely 2011).

Considering that many forensic laboratories perform drug profiling analysis using 'in-house' methods, discrimination of seizures perhaps remains limited at the national level. Given the present scenario whereby ATS drugs trafficking extends beyond regional boundaries, a harmonised method for comparative analysis of these drugs has since been suggested (Ballany et al. 2001; United Nations Office on Drugs and Crime (UNODC) 2014). In this context, the Harmonised methods for analysing amphetamine known as the Collaborative Harmonisation of Methods for the Profiling of Amphetamine-type Stimulants (CHAMP) for organic and inorganic profiling was first introduced by the European Commission authority (Aalberg et al. 2005a; Aalberg et al. 2005b; Andersson et al. 2007a, 2007b, 2007c; Lock et al. 2007). This robust method has enabled the exchange of forensic data at both national and international levels, making amphetamine drug profiling data readily comparable regardless of where the analysis is conducted therefore meaningful common link between seizures and understanding the route of trafficking can be effectively established. It would be interesting to see if the existing methods can be extended to similar type of ATS drugs for example methamphetamine so that linkages between ATS drugs are possible.

This paper aimed at demonstrating the feasibility of using the CHAMP method for impurity profiling (single extraction and chromatographic procedure) of amphetamine and methamphetamine drug seizures. Identification of impurities based on their mass spectral data to deduce the possible synthetic route is also demonstrated.

EXPERIMENTAL DETAILS

MATERIALS AND REAGENTS

Unless stated otherwise, all chemicals used in this study were purchased from Sigma® (Darmstadt, Germany). Buffer solution (1 M) was prepared by dissolving 121.1 g of Trizma-base (BDH Chemicals, Poole, England) in deionised water and its final pH was adjusted to 8.1 using hydrochloric acid (HCl) (1 M). Once the desired pH was achieved, deionised water was added to the 1 L volumetric mark and the pH was measured again using a calibrated pH meter (Hanna Instruments, pH 211). Adjustment to the desired pH was carried out either using HCl (1 M) or sodium hydroxide (NaOH) (1 M).

Four batches of amphetamine (labelled as sample A, B, C and D) and methamphetamine (labelled as E, F, G and H) synthesised samples submitted to the Centre for Forensic Science, University of Strathclyde from year 2004 to 2008 were analysed in this study. Samples were in dry powder form and have been kept in sealed vials stored in a secured drug cabinet at room temperature. Following the harmonised method described by Andersson et al. (2007b), these two drugs were extracted and analysed from the respective samples. Each batch was thoroughly homogenised using a mortar and pestle prior to sampling. The homogenised sample (200 mg) was weighted, dissolved in 4 mL buffer solution (pH8.1) and sonicated for 10 min. Upon completion, toluene (200 mL) with eicosane, (C₂₀) as the internal standard was added into the solution and sonicated for another 10 min, prior to centrifugation (3000 rpm for 5 min) to facilitate phase separation. The organic solvent phase was then removed and transferred into a GC vial for GC-MS analysis.

INSTRUMENTATION

Instrumental analysis was performed on a HP 6890 Gas chromatograph interfaced with HP 5973 mass spectrophotometer (MS) detector (HP Agilent, USA). The column used was an Rtx-5 capillary column (30.0 m × 0.25 mm diameter with film thickness 0.25 µm) (Restek, UK). Helium was used as the carrier gas at constant flow rate of 25 cm/s. The initial oven temperature was held at 60°C for 1 min and ramped up at 10°C/min to 300°C, and then held for 10 min at the final temperature, bringing the total analysis time of 35 min. Injection of sample (1 µL) was made using the splitless mode at 260°C. The scanning range was from 30-550 amu. The transfer line, the ion source and the quadrupole temperatures of the MS were set at 305°C, 230°C and 150°C, respectively. All the parameters reported here were in accordance with that of the CHAMP method indicated by the previous researchers (Andersson et al. 2007b).

IMPURITY PROFILING

Data obtained from the total ion chromatogram (TIC) profiles were compared across the samples in the

first instances. Impurities peaks were integrated for normalisation against the eicosane (C₂₀) internal standard peak area. Identifications of the peaks were made using the National Institute of Standards and Technology (NIST) mass spectral database (version 2.0f) (NIST 2008) available in the GC-MS system and also using previous literatures (Allan & Ely 2011; Andersson et al. 2007a; Bachs & Woo 2007; Cole 2003; Inohue et al. 2008; Kunalan et al. 2009; Puthaviriyakorn et al. 2002; Qi et al. 2006; Verweij 1989).

RESULTS AND DISCUSSION

The harmonised method showed chromatographic profiles (Figures 4 & 5) of the drugs samples, showing the active compounds as well as the impurities. In forensic drug profiling, identification of compounds especially the target impurities is important for determination of possible route of synthesis. Identification based on the mass spectral data showed that amphetamine can be identified at retention time (t_r) of approximately 17.5 min, while methamphetamine eluted at much earlier interval (at approximately 8.7 min). The %RSD values from the triplicate analyses of the amphetamine and methamphetamine samples ranged between 7.4-8.9% and 6.2-8.4%, indicating good reproducibility of the analytical method.

The results in Figures 4 and 5 illustrate the ability of the CHAMP method in detecting amphetamine and methamphetamine at retention time (t_r) of approximately 17.5 and 8.73 min, respectively. In addition, impurities in the amphetamine samples remained at considerably low concentrations due to the low abundance presented (Figures 4 & 5). Evidently, all the amphetamine samples (A, B, C and D) demonstrated similar chromatographic profiles. Except for sample H, similar chromatographic profiles were observed for the other methamphetamine samples (E, F and G). This discrepancy is common in seized sample as clandestine preparation hardly exercise quality control from one batch to another (Daeid et al. 2003). In general, fewer impurities were observed for the methamphetamine samples when compared with that of the amphetamine samples. Detection of impurities in synthetic drug although highly desired by forensic analyst, can sometimes be difficult due to the complexity of the sample itself, diverse chemical reactions that take place during synthesis as well as poor quality control especially amongst clandestine laboratories. Therefore, it is highly anticipated that variations especially in terms of chemical constituents exist in the final product as well as the addition of adulterants, diluents or cutting agents to the final product prior to distribution to the end users. Such factors and variations in impurities may prove useful in providing valuable background information to the forensic scientists about the seized samples and perhaps, their origin.

Alignment of all chromatograms of the amphetamine samples A, B, C and D showed the consistent presence of 25 compounds. Further examination of the spectral data of the impurity peaks showed vital information regarding possible synthetic route of the amphetamine samples

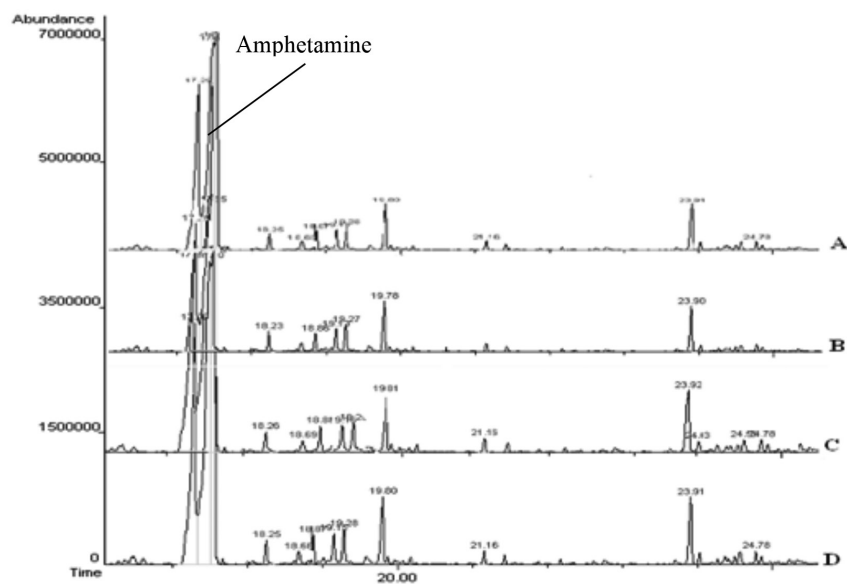


FIGURE 4. Total ion chromatograms (TIC) sections (to facilitate viewing of impurities) from the four amphetamine samples labelled as A, B, C and D

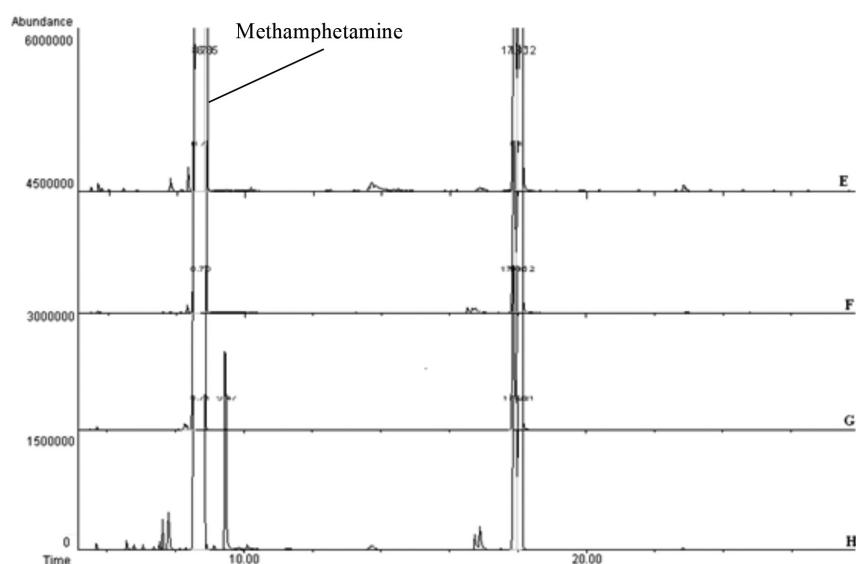


FIGURE 5. Total ion chromatograms (TIC) sections (to facilitate viewing of impurities) from the four methamphetamine samples labelled as E, F, G and H

although not all of the impurity peaks were successfully identified. Some of the impurities were identified by comparing their mass spectral information against the hydrocarbon mass spectral database (NIST- version 2.0f) available in the GC-MS system as well as related literatures (Allan & Ely 2011; Andersson et al. 2007a; Bachs & Woo 2007; Cole 2003; Inohue et al. 2008; Kunalan et al. 2009; Puthaviriyakorn et al. 2002; Qi et al. 2006; Verweij 1989). Identification of these impurities has helped to point out several important markers that are specific to drugs synthesized via certain routes. The presence of Leuckart's route specific marker of methylphenylpyrimidine as suggested by Cole (2003) was also detected, eluting at

approximately 12.548 min (Table 1). Other impurities *viz.* bis-(1 phenylisopropyl) amine, N-formylamphetamine and N, N-di (b-phenylisopropyl) amine were also detected at retention time (t_r) of approximately 17.526, 21.172 and 21.441 min, respectively (Table 1). Identification of these impurities attempted by aligning the chromatographic profiles of the amphetamine samples strongly suggested that they could be associated or had been synthesised using the Leuckart's route (Allan & Ely 2011; Cole 2003; Verweij 1989).

Considering that in this study the impurities in all the amphetamine and methamphetamine samples were identified by comparing their mass spectral data

TABLE 1. listed peak retention time, major mass spectrum ions and tentative identification of respective peaks from amphetamine samples

Peak Number	Retention Time (t _r) (mins)	Major Ions (m/z)	Tentative Identification
1	12.546	170, 102, 115	methyl-phenylpyrimidine
2	12.946	118,91,72,65	Unknown
3	16.446	91,134,65,120	unknown
4	16.926	178,165,152,91	unknown
5	17.269	91,162,119,65	unknown
6	17.526	162,91,119,65	bis-(1 phenylisopropyl)amine
7	17.652	91,134,65,117	unknown
8	18.252	179, 165,115,91	unknown
9	18.686	160, 91,143,128	unknown
10	18.880	160,91,143,128	unknown
11	19.149	143,160,91,128	unknown
12	19.275	143,160,91,128	unknown
13	19.795	120,91,115,103	unknown
14	20.172	258,244,91,115	unknown
15	21.172	91, 190,119,65,162	N-formylamphetamine
16	21.441	91,190,119,65	N,N-di (β-phenylisopropyl)amines
17	22.184	118,179,91,165	unknown
18	22.624	91,120,143,115,128	unknown
19	22.807	149,91,167	unknown
20	23.893	250,70,91,117,179	unknown
21	24.024	250,91,70,115,179	unknown
22	24.390	186,91,143,115,65,168	unknown
23	24.779	91, 115, 128,143	unknown
24	24.850	276,91, 115,65,128	unknown
25	25.385	91,215,115,77,65	unknown

against previously published literatures (Allan & Ely 2011; Andersson et al. 2007a; Cole 2003; Bachs & Woo 2007; Inohue et al. 2008; Kunalan et al. 2009; Puthaviriyakorn et al. 2002; Qi et al. 2006; Verweij 1989) and hydrocarbon database alone, without suitable comparisons with that of commercial pure standards (which are rarely available from commercial suppliers), the identification attempted may prove to be tentative. In this context it is pertinent to indicate here that this approach of tentative identification has been generally gaining acceptance within the body of literature (Bachs & Woo 2007; Inohue et al. 2008; Kunalan et al. 2009; Puthaviriyakorn et al. 2002; Qi et al. 2007, 2006). The chromatographic profiles of the methamphetamine samples (Figure 5) were evidently 'cleaner' with low abundance of impurities (Table 2) when compared to that of the amphetamine samples. Interestingly, P2P was identified in the samples at retention time (t_r) approximately 10.552 min, suggesting that the samples

could have been synthesised *via* Leuckart's, nitrostyrene, cold method or reductive amination routes. This was in agreement with the findings reported by Verweij (1989) that the reductive amination synthesis would lead to lesser with P2P being its specific impurity. Later study (Kunalan et al. 2009) further reaffirmed that P2P was the only route specific impurity for methamphetamine of reductive amination synthesis when acidic extraction was performed onto the drug. Since indication on the presence of P2P when basic extraction is performed onto these drugs remains unreported, suitable inference on the possible synthetic route for sample F and G could not be attempted. As these were clandestine preparations, many factors (e.g. variations during production, purity of the chemicals and also human skills) may contribute to the observed inconsistencies of the impurities (Daeid et al. 2003). Therefore, further studies involving larger sample sizes as well as geographical locations acquire forensic significance.

TABLE 2. Listed peak retention time, major mass spectrum ions and tentative identification of respective peaks from methamphetamine samples

Peak Number	RetentionTime (t _r) (mins)	Major Ions (m/z)	Tentative Identification
1	5.677	77,51,105,106	Unknown
2	7.077	79,77,51,106,91	Unknown
3	7.334	105,77,51,136	Unknown
4	9.546	72,91,65,77,148	Unknown
5	10.552	91,132,65,51	P2P
6	12.078	118,117,91,58,191	Unknown
7	16.313	132,91,118,77	Unknown
8	18.651	91,148,190,119,77	Unknown
9	19.457	105,77,162,91	Unknown
10	19.954	160,91,77,105	Unknown
11	22.017	149,57,167,71	Unknown

CONCLUSION

The use of harmonised methods for analysing these two types of phenethyl amine drugs i.e. amphetamine and methamphetamine prove feasible. Identification of route specific impurities in the amphetamine samples suggested that P2P was used as the starting material and the samples were synthesised by the Leuckart's route. Considering the similarities in the chromatographic profiles of samples A, B, C and D and the fact that 4-methyl-5-phenylpyrimidine, i.e. a specific impurity for Leuckart's route was found in all amphetamine samples, the possibility that the samples originated from the same source could not be ruled out. Although no conclusive identification could be made out for impurities in the methamphetamine samples, the presence of P2P is suggestive towards the possibility of synthetic route being either Leuckart's, nitrostyrene or aminative reduction pathway. This study demonstrates that impurity profiling of illicit drugs with regard to synthesis route is useful to establish possible connections between drug seizures. Further studies on similar samples profile using amphetamine harmonised and other practised methods may be useful for comparing the effectiveness of extraction.

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