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Identification of impurities and statistical classification of methamphetamine hydrochloride drugs seized in the China

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Abstract

A total of 48 methamphetamine hydrochloride samples from eight seizures were analyzed using gas chromatography–mass spectrometry (GC–MS) and a flame ionization detector (GC–FID).

Major impurities detected include 1,2-dimethyl-3-phenylaziridine, Ephedrine/pseudoephedrine, 1,3-dimethyl-2-phenylnaphthalene, 1-benzyl-3-methylnaphthalene. These data are suggestive of ephedrine/pseudoephedrine as the main precursor of the methamphetamine hydrochloride samples seized during 2006–2007. Additionally the presence of 1,3-dimethyl-2-phenylnaphthalene, 1-benzyl-3-methylnaphthalene is indicative that six seizures were synthesized via the more specific ephedrine/hydriodic acid/red phosphorus method.

In addition, five impurities were found for the first time in methamphetamine hydrochloride samples. Seventeen impurity peaks were selected from the GC–FID chromatograms. The peak areas of the selected peaks were then grouped for cluster analysis.

Keywords

Methamphetamine hydrochloride; Profiling of impurities; Cluster analysis

1. Introduction

Due to the increasing number of drug cases, as well as the widening globalization of illicit drugs, law enforcement agencies worldwide have adopted the strategy of profiling of drug impurities. Detailed impurity information has been reported on the methamphetamine drugs seized in countries such as the European Commission [1], Japan [2,3], Thailand [4], Korea [5,6], the Philippines [7] and Australia [8,9], where methamphetamine abuse is one of the most serious drug issues.

The information obtained can be used to establish drug trafficking patterns and distribution networks, and to identify methods used in the manufacture of illicit drugs. Methamphetamine hydrochloride is currently one of the most widely used illicit drugs in the China. However, in the open literatures there has been little information available on impurity characteristics or profiling of methamphetamine drug seizures in China.

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The main objective of this work is to obtain impurity characteristics of the methamphetamine hydrochloride drugs and to identify synthetic routes and the trend in recent years providing forensic intelligence product to the Beijing Public Security Bureau (BPSB) intelligence group.

2. Materials and methods

2.1. Sample preparation

Methamphetamine hydrochloride crystals were ground and homogenized. Fifty milligrams were dissolved in 1 mL of buffer solution (four parts 0.1 M phosphate buffer of pH 7.0 and one part 10%, w/v, Na_2CO_3). The solution was extracted by vibrating for 5 min with 0.5 mL of ethyl acetate containing four n-alkanes (C10, C15, C20 and C28) as internal standards at 0.02 mg/L. After centrifuging the solution for 5 min at 3000 rpm, the organic layer was transferred into a glass insert of GC microvial for automatic sampling, and 1 μL was injected on the GC–FID and GC–MS analysis.

2.2. Reagents and chemicals

Buffer chemicals, sodium dihydrogen phosphate dihydrate ($\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$), disodium hydrogen phosphate dodecahydrate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$) and sodium carbonate (Na_2CO_3), were analytical grade, sourced from Beijing Chemical Reagent Ltd. (China). HPLC grade ethyl acetate solvent was sourced from Tedia Company, Inc. (USA). Internal standards, n-alkanes (C10, C15, C20 and C28), were sourced from Fluka. (USA).

2.3. Data analysis

Processing of GC–FID peak areas were performed in GC Chemstation (Agilent Technologies Co.) and Excel 2003 (Microsoft Co.). Cluster analysis and other statistical calculations were carried out in SPSS 13.0 (SPSS Inc.). Each peak area was calculated relative to IS3 and common logarithms of 1000 times their relative areas were used for the calculation of Euclidean distance between the samples, and the classification of the samples was visualized by hierarchical cluster analysis via the Ward method.

2.4. GC conditions

GC conditions of the GC–FID and GC–MS were the same. The oven temperature was programmed as follows: initial temperature was 50°C held for 1 min, followed by an increase of 10°C/min to 300°C, and then held for 10 min. The injector and detector (transfer line) temperatures were set at 230 and 300°C, respectively. Nitrogen was used as a carrier gas at a constant column flow rate of 2 mL/min. One microliter of the extracts was injected in the pulsed splitless (PS/L) mode.

2.5. Instruments

MS2 vibrating shaker (IKA Co., China manufactory) was used for extraction of organic impurities, and a 2420 centrifuge (KUBOTA Co., Japan) was used for centrifugation. Gas chromatographic (GC) analysis was carried out on a Hewlett-Packard HP6890N GC equipped with an FID and an HP7683 automatic sampler. GC–MS analysis was carried out on a Trace GC Ultra equipped with a Polaris Q mass selective detector (MSD) and an AS3000 automatic sampler. The MSD was operated in the electron impact (EI) mode at 70 eV. Scan mode was used as an acquisition mode, and the mass ranges were 35–450 (m/z). The GC–FID and GC–MS were equipped with a DB-5 capillary column (30 m×0.32 mm×1.0 μm film thickness) (Agilent Technologies Co., USA).

3. Results

Eight seizures of Methamphetamine hydrochloride from BPSB captured between 2006 and 2007 were analyzed. Typically the seizures were crystals and had a purity of more than 95%. Each of seizures weighed over 400g and belonged to a bag. The contents of each selected bag (seizure) were divided into six samples. Thus, a total of 48 samples were obtained. 10g were weighed out from each sample and crushed. Fifty milligrams were taken for analysis. The each sample was analyzed three times to determine the variability within each seizure and whether the samples from the same bag (seizure) belong to the same batch. Table 1 lists the main impurities found, and their characteristic MS ions found as a result of GC–MS analysis. The numbers associated with the compounds correspond with the annotated peaks in Fig. 1.

The results show that generally impurity profiles of methamphetamine samples in the same seizure show more similarities than that in different seizures,

Typical gas chromatograms of the ethyl acetate extracts of methamphetamine samples are shown in Fig. 1. Peaks #1, #2, #4, #5, #7, #8, #9, #12, #15, #16, #18, #19, #21, #22 and #23 were confirmed to be Toluene, Benzaldehyde, cis-1,2-Dimethyl-3-phenylaziridine, 1-Phenyl-2-propanone/Amphetamine, N-Ethylamphetamine, N,N-Dimethylamphetamine, Ephedrine/pseudoephedrine, N-Acetyephedrine, 3,4-Diphenyl-3-buten-2-one, N,N-di-(β -Phenylisopropyl)amine (two stereoisomers), 1,3-Dimethyl-2-phenyl-naphthalene, 1-Benzyl-3-methylnaphthalene, Me(α -Me-Ph)amino-1-Ph-2-propanone (two stereoisomers), Benzoylmethamphetamine and N,N-di-(β -Phenylisopropyl)formamide by GC-MS, respectively, from the comparative analysis of respective peak retention time and mass spectral data with those of authentic compounds or literatures. Fig. 2 shows EI mass spectra of peaks #6, #11, #13, #14 and #20, which are new impurities found.

Amphetamine, #2 and #8 are impurities produced in the process of extraction [10] or the pyrolysis products under the high temperature of GC injector [11,12]. The 1-Phenyl-2-propanone (**P2P**) co-eluted with Amphetamine.

After excluding troublesome and non-characteristic peaks, the 17 peaks (in Table 2) were selected and were applied for cluster analysis. Similarity and/or dissimilarity of the chromatographic profiles between samples were evaluated using the Euclidean distances of 17 relative peak areas after common-logarithmic transformation. Fig. 3 shows the distribution of distances between the profiles obtained from the same seizure, as well as those from different seizures. Out of 120 pairs of intra-seizure distances, none overlapped with the range of inter-seizure distances. A dendrogram obtained from a hierarchical cluster analysis of 48 sample profiles also shows that the same seizure profiles were well grouped (Fig. 4). The samples from the same bag (seizure) possibly belong to the same batch. Intra- and inter-laboratory reproducibility is now in progress. It is well known that there are several statistical indices for computerized comparison. Further statistical analyses are currently under investigation.

4. Discussion

4.1. Optimization of analytical procedure

The validity and use of GC and GC–MS methodologies for the analysis of methamphetamine drugs have been well covered in the literatures with considerable methods development and optimization reported. The use of the medium bore column with 1 μ m film thickness was justified by Inoue et al. [13].

Preliminary experiments were performed to optimize the analytical procedure. There are many artifact impurities arising from the preparation of samples and conditions of GC. Moreover,

some artifacts pose a barrier to the statistical processing of methamphetamine profiling. Sasaki and Makino [3] investigated capillary GC analysis using pulsed splitless(PS/L) injection to minimize the thermal decomposition of impurities at the injection port and improve the transfer of samples into the column. The effective conditions for PS/L-mode were confirmed to be 230 °C and 50psi. The high reproducibility of this analytical method thus enables the reliability of statistical analysis to be enhanced.

4.2. Identification of impurities

For impurities with certified standards available, identification was based on the match of both the retention time and mass spectrum of an unknown peak with that of the standard. This approach allowed toluene to be identified in the seized samples. Other impurities were identified via comparison with known literatures reports. Thus, the mass spectrum and retention time associated with #2, #4, #5, #7, #8, #9, #12, #16 and #23 are consistent with data reported by Qi Y et al. [8,9]. The mass spectrum and retention time associated with #15, #21 and #22 are consistent with data reported by Dujourdy L et al. [1].

Compounds #18 and #19 correlate well with 1,3-Dimethyl-2-phenylnaphthalene and 1-Benzyl-3-methylnaphthalene, synthesized by Lee JS et al. [5] using α -acetylphenylacetonitrile with hydriodic acid/red phosphorus. The compounds #24, #25, #26, #27 and #28 were also observed by Lee JS et al. [5]

Exhaustive literatures searching and spectral analysis failed to identify compounds associated with peaks #6, #11, #13, #14 and #20. No evidence of similar spectra was found associated with impurities in methamphetamine or any other common illicit drugs. Interestingly compound #11 has the same major ions as #16.

4.3. Route identification

The samples are expected to provide important information to help with the identification of synthetic routes. Determination of the synthetic route in methamphetamine profiling relies on the identification of key, route specific marker impurity compounds. Leuckart reaction and reductive amination of **P2P** and various routes starting from ephedrine or pseudoephedrine are the most commonly used methods in clandestine laboratories [14-15]. Characteristics of impurities in methamphetamine over the years have been utilized to identify synthetic route. While the presence of ephedrine/pseudoephedrine may indicate a synthetic route via ephedrine, **P2P** is a non-specific marker for both reductive amination and the Leuckart reaction since it is also a by-product of the ephedrine route [16]. Evidentially **P2P** has been found in methamphetamine synthesized from ephedrine [17,18]. Ephedrine/pseudoephedrine appeared in Fig. 1(a), which presumably indicates an ephedrine origin of this sample.

Impurities consistent with the ephedrine route included 1,2-dimethyl-3-phenylaziridine, 1,3-dimethyl-2-phenylnaphthalene and 1-benzyl-3-methylnaphthalene. The two naphthalenes are considered specific of the ephedrine/hydriodic acid/red phosphorus route.

The 1,2-dimethyl-3-phenylaziridines are considered marker compounds of the ephedrine route as they are found only in methamphetamine synthesized from ephedrine/pseudoephedrine and their formation is closely related to ephedrine or pseudoephedrine. It is proposed that during the synthesis, the haloephedrine intermediates (chloroephedrine, if via the **Emde** route, or iodoephedrine, when using hydriodic acid/red phosphorus) undergo an internal substitution reaction, or ring closure, losing chlorine or iodine to produce the cis- and/or trans-aziridines [9,16,17]. The chromatogram shown in Fig. 1(a) illustrates a typical profile of ephedrine precursor with cis-1,2-dimethyl-3-phenylaziridine present.

Furthermore, according to Cantrell et al. [16], under the acidic conditions associated with the hydriodic acid/red phosphorus method, the aziridines undergo ring opening producing the **P2P** intermediate, with subsequent self-condensation and dehydration of two **P2P** molecules affording 1,3-dimethyl-2-phenylnaphthalene and 1-benzyl-3-methylnaphthalene. Given that the **P2P** intermediate does not occur under non-acidic conditions, such as the ephedrine route via chloroephedrine, the naphthalenes are considered characteristics of the hydriodic acid/red phosphorus ephedrine route [16,17]. Fig. 1(a, b, c and e) show the profile of a methamphetamine samples synthesized via this route.

#16 and #23 are among the most common impurities arising via the Leuckart route and/or reductive amination [19]. However, they are identified in methamphetamine containing explicit ephedrine route markers such as aziridines and naphthalenes #18 and #19. It is interesting, as shown in Fig. 1(a, b, c and e), that the peak intensities of the naphthalenes #18 and #19 increase as that of the #16 decrease and *vice versa*. This variation is particularly significant, for it seems that the two types of impurities are generated from competitive processes. [9]

To summarize, except for two seizures we have been unable to identify the synthetic route, all other seizures contain evidence they were produced via ephedrine/pseudoephedrine. From the results we can deduce the conclusion that ephedrine/pseudoephedrine is the primary chemical precursor to synthesize methamphetamine in recent years in china.

5. Conclusion

The present method offers superior separation of impurities in methamphetamine hydrochloride crystals using chromatographic techniques. The 17 peaks selected were characteristic and diagnostic for the classification and comparison of chromatograms. The Euclidean distance of 17 relative peak areas after logarithmic transformation was effective for the evaluation of similarity and/or dissimilarity of impurity profiles. The preliminary work shows that it is very useful for getting intelligence from methamphetamine impurity profiling.

Information about the impurities in methamphetamine allowed identification of the drug synthetic routes. In the drugs manufactured via the ephedrine route where the marker compounds, the aziridines or naphthalenes, were present distinctively. However, in some cases for the high purity methamphetamine, this information alone is insufficient to indicate any specific clandestine manufacturing route. We are actively pursuing the identities of the unknown impurities via synthetic approach and will report the outcomes of our efforts in due course.

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Fig. 1.
Typical GC–FID chromatograms of the samples.

Fig.2.
Mass spectra of newly found impurities: (a) peak 6; (b) peak 11; (c) peak 13; (d) peak 14; (e) peak 20.

Fig.3.

Distribution of distances between sample profiles from intra-seizure (left) and between sample profiles from inter-seizure (right), as measured by Euclidean distance.

Fig.4.

Dendrogram obtained from a cluster analysis of 48 methamphetamine sample impurity profiles from eight different seizures.

Table 1
Impurities detected in China methamphetamine samples

Compound no.	Name	RRt ^a	Major ions
1	Toluene	4.327	91, 92
2	Benzaldehyde ^b	8.568	105, 77, 51, 106
3	IS1 (C10)	9.134	
4	cis-1,2-Dimethyl-3-phenylaziridine ^b	11.324	146, 105, 132
5	1-Phenyl-2-propanone/ Amphetamine ^b	11.472	146, 105
6	Unknow	13.329	44, 150, 72, 91
7	N-Ethylamphetamine ^b	13.408	72, 44, 91
8	N,N-Dimethylamphetamine ^b	13.748	72, 91
9	Ephedrine/pseudoephedrine ^b	15.323	58, 77, 105
10	IS2 (C15)	16.434	
11	Unknow	17.733	91, 162, 119, 44
12	N-Acetylphedrine ^b	17.928	58, 100
13	Unknow	18.079	117, 118, 91
14	Unknow	18.790	70, 128, 44, 91
15	3,4-Diphenyl-3-buten-2-one ^b	20.797	178, 179, 221, 222, 152
16	N,N-di-(β-Phenylisopropyl)amine (two stereoisomers) ^b	21.392	91, 162, 119, 44
17	IS3 (C20)	21.871	
18	1,3-Dimethyl-2-phenylnaphthalene ^b	22.934	217, 232, 202,
19	1-Benzyl-3-methylnaphthalene ^b	23.135	217, 232, 202
20	Unknow	23.284	91, 159, 131, 115
21	Me(α-Me-Ph)amino-1-Ph-2-propanone (two stereoisomers) ^b	23.290	91, 120, 105, 190, 238, 146
22	Benzoylmethamphetamine ^b	23.380	105, 162, 77, 91
23	N,N-di-(β-Phenylisopropyl)formamide ^b	24.322	91, 190, 162, 119
24	Unknow ^b	25.176	115, 249, 178, 264
25	Unknow ^b	25.322	58, 91, 190
26	Unknow ^b	26.290	168, 167, 91, 126
27	Unknow ^b	26.513	168, 167, 91, 126
28	Unknow ^b	26.609	168, 167, 91, 126
29	IS4 (C20)	29.227	

^aRelative retention time

^bThese impurities are mentioned in Ref. [8] for 2, 4, 5, 7, 8, 9, 12, Ref. [1] for 15, 21, 22, Ref. [9] for 16, 23, Ref. [5] for 18, 19, 24, 25, 26, 27, 28.

Table 2

Impurities used for data processing

Compound no.	Name
1	Toluene
4	cis-1,2-Dimethyl-3-phenylaziridine
6	Unknow
7	N-Ethylamphetamine
8	N,N-Dimethylamphetamine
9	Ephedrine/pseudoephedrine
11	Unknow
12	N-Acetyephedrine
15	3,4-Diphenyl-3-buten-2-one
16	N,N-di-(β -Phenylisopropyl)amine
18	1,3-Dimethyl-2-phenylnaphthalene
19	1-Benzyl-3-methylnaphthalene
24	Unknow
25	Unknow
26	Unknow
27	Unknow
28	Unknow