

Impurity profiling of methamphetamine hydrochloride drugs seized in the Philippines

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Abstract

Methamphetamine hydrochloride is one of the most widely used illicit drugs in the Philippines. In this study, we describe the application of cluster analysis of trace impurities in the profiling of the seized methamphetamine drug samples.

Thirty milligrams of a homogenized drug sample were dissolved in 1 mL of pH 10.5 buffer solution and extracted with ethyl acetate containing three internal standards. The trace impurities were identified using gas chromatography–mass spectrometry (GC–MS) and quantified by gas chromatography with a flame ionization detector (GC–FID).

Following previously reported methodologies, 30 impurity peaks were selected from the GC–FID chromatograms. The peak areas and retention times were referenced to the internal standards. The peak areas of the selected peaks were then grouped for cluster analysis. In order to check for consistency of clustering, two further cluster analyses were performed using 40 and 50 impurity peaks. Changes in clustering were observed in going from 30 to 40 impurity peaks, while analyses using 40 and 50 impurity peaks gave similar results. Thus, for the seized drug samples used in this study, cluster analysis using at least 40 impurity peaks showed better consistency of clustering as compared to analysis using 30 peaks only.

Ten of the impurity peaks were identified, of which four were identified for the first time in methamphetamine drug samples. These are *p*-bromotoluene, *N*-benzyl amphetamine, *N*-ethyl amphetamine, and *N*-ethyl methamphetamine. The presence of phenyl-2-propanone (P2P), *N,N*-dimethyl amphetamine, and *N*-formyl amphetamine is indicative that these casework samples were synthesized using the Leuckart method.

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1. Introduction

Methamphetamine hydrochloride is currently one of the most widely used illicit drugs in the Philippines. During the first quarter of 2002 alone, about 41,220 kg of methamphetamine hydrochloride were seized and two clandestine drug laboratories were raided [1]. Due to the increasing number of

drug cases, the proliferation of clandestine laboratories, as well as the widening globalization of illicit drugs, law enforcement agencies worldwide have adopted the strategy of profiling of drug impurities [2]. 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.

In this work, we describe the identification of trace impurities in seized methamphetamine samples using gas chromatography–mass spectrometry (GC–MS) and their quantification using gas chromatography with a flame ionization detector (GC–FID). The GC–FID data were used in the profiling of the drug samples using cluster analysis.

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Table 1
List of 30 sample caseworks used in this study and place of seizure

Sample caseworks	Place of seizure
961, 961C	Pangasinan
280, 281, 282, 283, 284, 285, 286, 288, 289, 290, 292, 293, 295	Zambales
636, 637, 638, 639	Quezon Province
271A, 271A1, 272, 273A, 273B, 276A, 276B, 276C, 276D, 278A, 278A2	Metro Manila

2. Materials and methods

2.1. Sample preparation

Table 1 gives the list of drug samples used in this study. The samples were taken from 30 caseworks of seized methamphetamine drug samples, each of which weighed over 2 kg. All samples were crystalline in form. Using the UNDCP rule, \sqrt{n} bags (where n is the total number of bags in the seizure) were randomly selected for sampling [3]. The contents of each selected bag were quartered, and then 5 g were weighed out. The 5 g samples from each of the bags were mixed together and the mixture was then crushed. Thirty milligram were taken for analysis. Variability within each seizure was not determined.

Thirty milligrams of each drug sample were dissolved in 1 mL of pH 10.5 buffer solution and extracted with 200 μ L of ethyl acetate containing 35 mg/L of diphenylamine (Merck), 25 mg/L of *n*-tridecane (Aldrich), and 20 mg/L of *n*-tetracosane (Sigma) as internal standards. The mixture

was centrifuged and the organic layer was transferred to a vial for GC analysis. The samples were analyzed on the day of extraction.

Blank samples containing solvent and internal standards were run to check for background impurities. The sequence of injection was patterned after the UNDCP recommended procedure [3]: solvent, reference standard, blank sample, sample extract (trial 1), solvent, sample extract (trial 2), solvent and sample extract (trial 3).

The relative retention times of the impurity peaks were calculated based on the retention time of *n*-tridecane [4]. The relative peak areas, on the other hand, were calculated based on the closest eluting internal standard.

2.2. Gas chromatography analysis

A GC–FID (HP 5890 Series II GC) equipped with a HP-1 capillary column (25 m \times 0.2 mm \times 0.33 μ m film thickness) was used for quantification of impurity peaks. The carrier gas was nitrogen at a flow rate of 1.4 mL/min. The GC was operated in the splitless mode and sample injection was 1 μ L. The injector and detector temperatures were maintained at 250 and 300 $^{\circ}$ C, respectively. The oven temperature program was as follows: initial temperature at 50 $^{\circ}$ C for 1 min, increase at 10 $^{\circ}$ C/min to 300 $^{\circ}$ C, and hold for 4 min.

The GC–FID data were transferred to a Microsoft ExcelTM 2000 spreadsheet to calculate the relative retention times, t_R' , and percentage relative peak areas. Euclidean distances were calculated using the percentage relative peak areas of the selected peaks and were clustered using Clustan GraphicsTM (Scotland, UK).

Table 2
Sample tabulation of the peaks from casework 639. (See footnote for explanation)

Retention time			Peak area		
Time ^a (min)	Time ^b (min)	t_R' ^c	Peak area	Relative peak area (%) ^d	Group value ^e
3.16	3.160	0.2757	6731996.25	838146.94	6
3.59	nd	–	–	0.00	0
11.46 (IS)	11.460	1.002	803.20	1 00.00	–
11.67	nd	–	–	0.00	0
11.93	11.940	1.0419	19.05	2.00	1
12.42	12.390	1.0811	1931.90	203.23	3
15.41 (IS)	15.410	1.3447	950.60	100.00	–
15.86	nd	–	–	0.00	0
16.30	nd	–	–	0.00	0
16.57	16.560	1.4450	0.0009	0.00	1
17.60	17.540	1.5305	300.05	17.22	2
24.75 (IS)	24.750	2.1597	1742.65	100.00	0

^a Column 1 lists nine of the 40 peaks which were selected for cluster analysis.

^b Column 2 is a list of the peaks obtained from casework 639. Not all of the 40 peaks are present in all caseworks.

^c t_R' , relative retention time, where: $t_R' = (\text{retention time of peak from casework})/(\text{retention time of } n\text{-tridecane})$.

^d Relative peak area (%) = (area of selected peak)/(area of IS peak) \times 100. The relative retention time is used to compare the retention times of the peaks from the various caseworks.

^e See Table 3 for group values.

The impurities were identified using a GC–MS. The GC was a Hewlett-Packard 5890 and the MS was a Finnigan MAT 95ST mass spectrometer. The GC column used was DB-1 (50 m × 0.25 mm i.d. × 0.25 μm film thickness). The GC–MS was operated in the splitless mode; helium (ultra high purity, CIGI) was used as carrier gas. The injection port and transfer line temperatures were both set to 250 °C. The oven temperature program was the same as that used for the GC–FID analysis.

The mass spectrometer was operated in electron impact (EI) mode at 70 eV and 1000 resolution. Compound identification was done using the NIST 62,000 MS library. Only peak matches with reverse fit (rfit) values greater than 800 (maximum value is 999) were considered. The observed EI–MS fragmentations were compared with expected mass fragmentation patterns to check for

Table 3

Group values of peaks assigned from relative peak areas (%)

Relative peak area (%)	Group value
0	0
0 < x ≤ 10	1
10 < x ≤ 100	2
100 < x ≤ 1 000	3
1000 < x ≤ 10 000	4
10 000 < x ≤ 100 000	5
100 000 < x ≤ 1 000 000	6
Over 10 000 000	7

reasonableness of the identification. Impurity peaks could not be isolated due to the limited amounts of sample available for analysis.

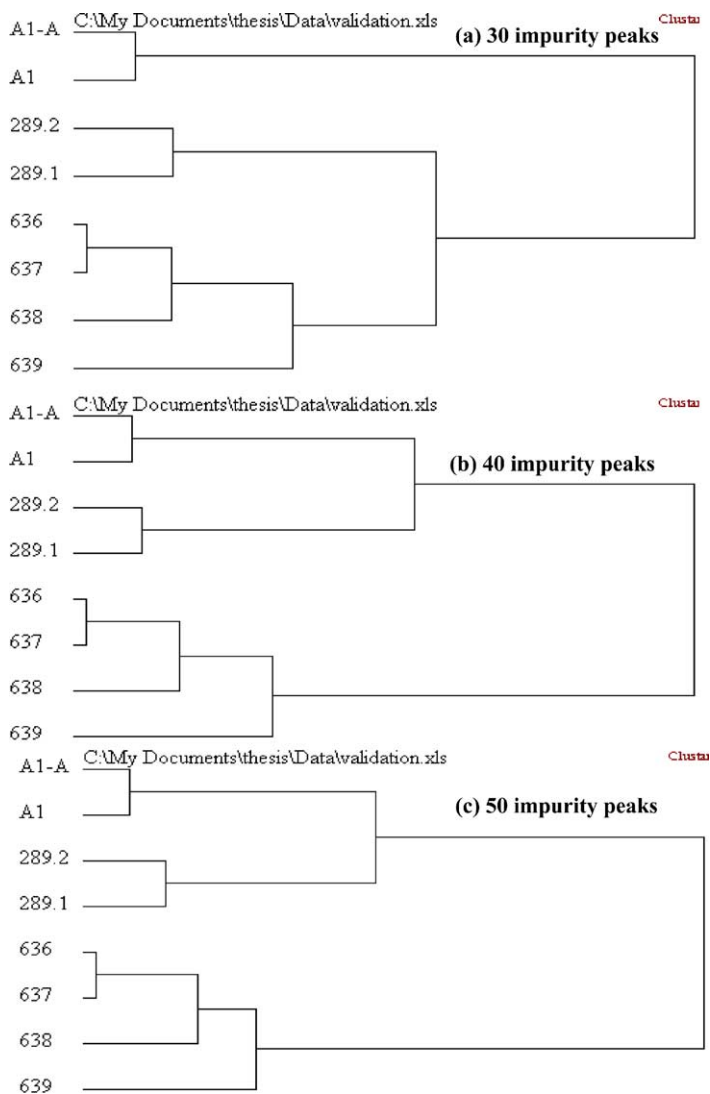


Fig. 1. Dendrograms for cluster analysis using (a) 30, (b) 40, and (c) 50 impurity peaks.

3. Results

3.1. Quantification of impurities using GC–FID

All of the impurity peaks in each of the 30 casework drug samples were tabulated and their relative retention times were calculated and compared. From this list, the most common peaks were selected for profiling and clustering. Not all of the impurities were present in all samples.

A partial list of impurity peaks with their corresponding relative retention times and relative peak areas is shown in Table 2. The relative peak areas of the selected impurity peaks were grouped according to Table 3. The group value for each sample was used for cluster analysis.

3.2. Consistency of clustering

Cluster analysis was carried out using the Clustan Graphics software. To check the consistency of the clustering, an experiment was conducted using samples from three large drug seizures. The three sets of samples were divided into eight different caseworks with the following codes: set A: 636, 637, 638, and 639; set B: A1–A and A1; and set C: 289.1 and 289.2. Following previously reported methodologies [5,6], 30 impurity peaks were selected from the GC–FID chromatograms and used for cluster analysis (Fig. 1(a)). In order to check for consistency of clustering,

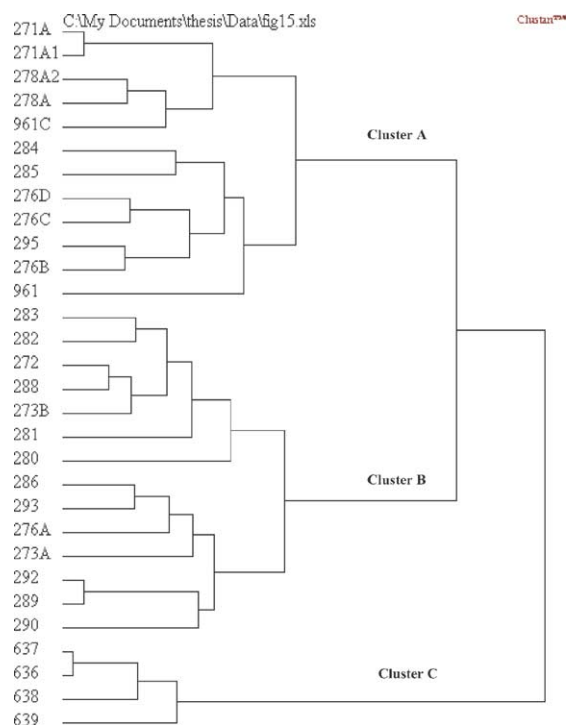


Fig. 2. Dendrogram of 30 caseworks using 40 impurity peaks and the clusters obtained from the analysis.

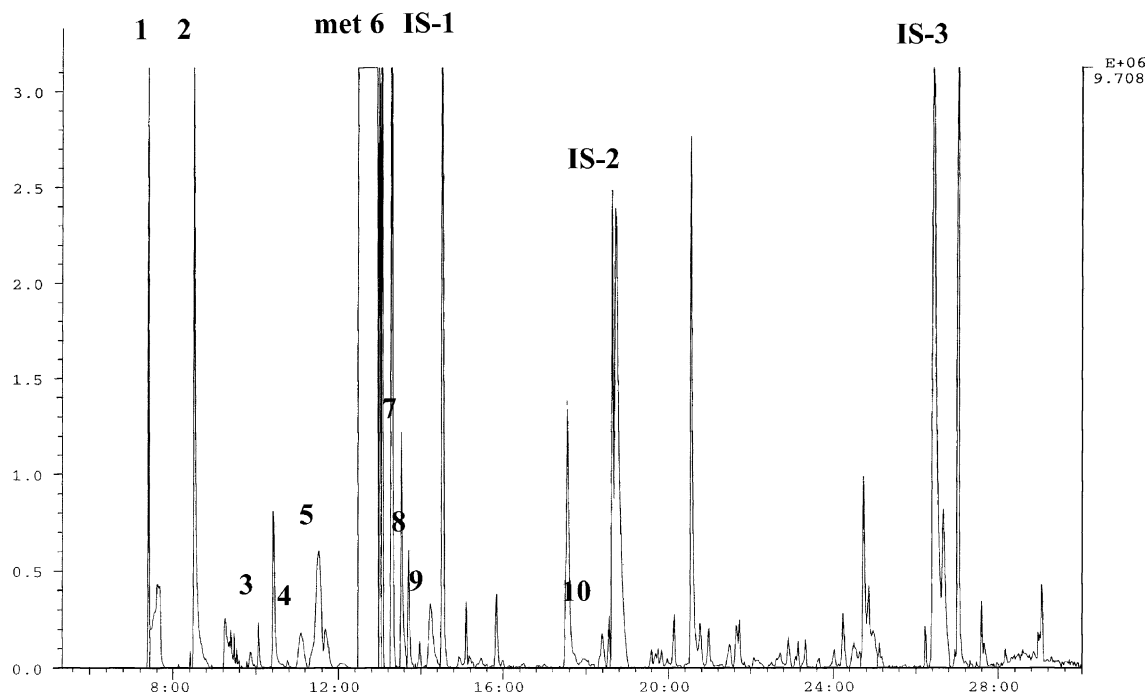


Fig. 3. Identification of impurity peaks by GC–MS from casework 639. Identified impurities are as follows. (1): Acetic acid; (2): benzaldehyde; (3): *p*-bromotoluene; (4): *N*-benzyl amphetamine; (5): phenyl-2-propanone; (Met): methamphetamine; (6): *N*-ethylamphetamine; (7): *N*-methylmethamphetamine; (8): *N*-ethylmethamphetamine; (9): *N*-formylmethamphetamine; (IS-1): *n*-tridecane; (10): *N*-acetyl methamphetamine; (IS-2): diphenylamine; (IS-3): *n*-tetracosane.

Table 4

Ten impurity peaks which were identified by GC–MS and their MS reverse fit values (rfit). See Fig. 3 for GC–MS chromatogram

Compound	rfit	Comments
Acetic acid (1)	982	Used as one of the reagents in the manufacture of methamphetamine using phenyl-2-propanone (P2P) as a starting material
Benzaldehyde (2)	980	Used as starting material in the synthesis of P2P
<i>p</i> -Bromo toluene (3)	876	Not identified in previous studies
<i>N</i> -Benzyl amphetamine (4)	920	Not identified in previous studies
Phenyl-2-propanone (5)	938	Common intermediate in the synthesis of methamphetamine by the Leuckart method or by reductive amination
<i>N</i> -Ethyl amphetamine (6)	925	Not identified in previous studies
<i>N</i> -Methyl methamphetamine (7) (<i>N,N</i> -Dimethylamphetamine)	936	Its occurrence could be due to contamination of methylamine or <i>N</i> -methylformamide with <i>N,N</i> -dimethylformamide [9]
<i>N</i> -Ethyl methamphetamine (8)	837	Not identified in previous studies
<i>N</i> -Formyl methamphetamine (9)	824	Methamphetamine produced by the Leuckart reaction often contains this compound as a result of incomplete hydrolysis [8]
<i>N</i> -Acetyl methamphetamine (10)	967	May form during precipitation of methamphetamine in the presence of an acetate moiety, such as acetic acid, ammonium acetate or ethyl acetate. [8,9]

additional cluster analyses were carried out using 40 and 50 impurity peaks (Fig. 1(b and c), respectively). The related casework samples were grouped as expected; however, the higher clusters were grouped differently when using 30 impurity peaks versus 40 and 50 impurity peaks; the results obtained for 40 and 50 peaks were very similar to each other. This suggests that the use of at least 40

impurity peaks yields more stable clustering results than 30 peaks.

3.3. Cluster analysis of seized drug samples

Table 1 lists the 30 drug caseworks used in this study with their places of seizure. These places include Metro Manila,

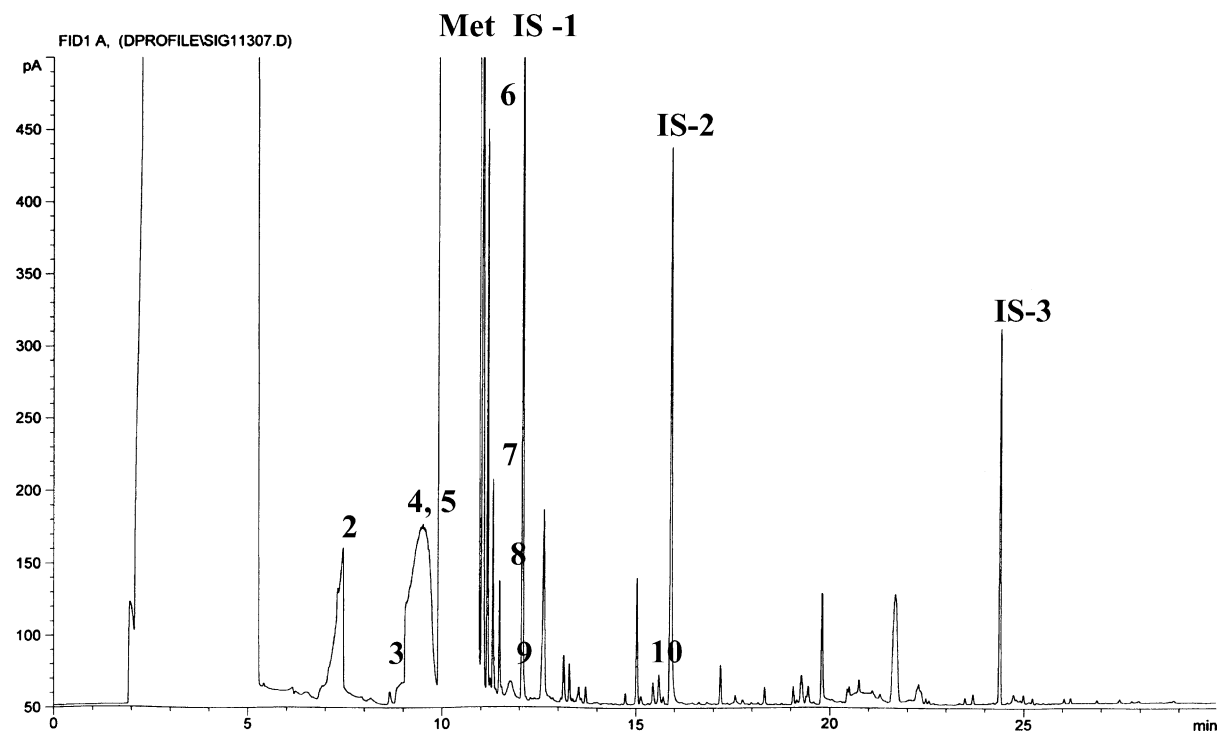


Fig. 4. Typical GC–FID chromatogram of casework 290. Peak numbers refer to the identities as determined by GC–MS (see Fig. 3). Note that not all impurities are present in all samples.

Pangasinan, Zambales, and Quezon Province. The 30 caseworks were clustered using 40 selected impurity peaks (Fig. 2). Cluster analysis revealed there were three major clusters and five minor clusters. It can be also noted that there appears to be a pattern with respect to the place of seizure. Samples seized in Pangasinan, Zambales, and Metro Manila were distributed in clusters A and B, while the samples seized in Quezon Province were all grouped in cluster C.

The accuracy of the cluster analysis was demonstrated when it was able to correctly group caseworks 271A and 271A1. Although these caseworks were obtained in two separate police operations, these samples were subsequently independently determined to have come from the same source.

3.4. Identification and frequency of occurrence of impurity peaks

Ten impurity peaks were identified by GC–MS (Fig. 3 and Table 4). Of the ten impurities, the following four compounds have not been previously reported: *p*-bromotoluene (3); *N*-benzyl amphetamine (4); *N*-ethyl amphetamine (6); and *N*-ethyl methamphetamine (8). The impurity peaks were located in the GC–FID chromatograms using their relative retention times, t_R' , based on the internal standard *n*-tridecane (Fig. 4).

4. Discussion

The frequency of occurrence of the identified impurities and their relative percentage content in the 30 caseworks used in this study are given in Table 5. The following impurities were detected in over 95% of the samples: *N*-benzyl amphetamine (4); phenyl-2-propanone (P2P) (5); *N*-ethyl amphetamine (6); *N*-methyl methamphetamine (7); *N*-ethyl methamphetamine (8); *N*-formyl methamphetamine

Table 5

Frequency of occurrence in seized samples and average amount of identified impurities in the 30 caseworks used in this study

Compound	Frequency of occurrence (%)	Average amount ($\mu\text{g/g}$)
Acetic acid (1)	53.3	1.05
Benzaldehyde (2)	86.7	1.62
<i>p</i> -Bromotoluene (3)	73.3	2.46
<i>N</i> -Benzyl amphetamine (4)	96.7	21.4
Phenyl-2-propanone (5)	93.3	8.59
<i>N</i> -Ethyl amphetamine (6)	100.0	16.4
<i>N</i> -Methyl methamphetamine (7)	96.7	46.3
<i>N</i> -Ethyl methamphetamine (8)	93.3	10.4
<i>N</i> -Formyl methamphetamine (9)	100.0	0.68
<i>N</i> -Acetyl methamphetamine (10)	100.0	4.88

(9); and *N*-acetyl methamphetamine (10). A trace amount of acetic acid (1) was present in about half of the samples, while benzaldehyde (2) and *p*-bromotoluene (3) were present in more than 70% of the samples. Among all of the impurities identified, *N*-methyl methamphetamine (7) was found in the highest concentration (average of 6.9 ppm in 97% of samples).

The presence of phenyl-2-propanone in all of the drug samples suggests that the Leukart method was the common procedure used. The presence of benzaldehyde (2) in almost 87% of the drug samples suggests that this may be the starting material used for the synthesis of P2P via the reaction of benzaldehyde with nitroethane followed by hydrogenation with Fe/HCl [7] (Fig. 5).

The formation of *N*-methyl methamphetamine (7), *N*-formyl methamphetamine (9), and *N*-acetyl methamphetamine (10) have been previously described [8,9]. *N*-methyl methamphetamine (7) may form in the presence of *N,N*-dimethylformamide as a contaminant. The presence of *N*-formyl methamphetamine (9) is indicative that the process

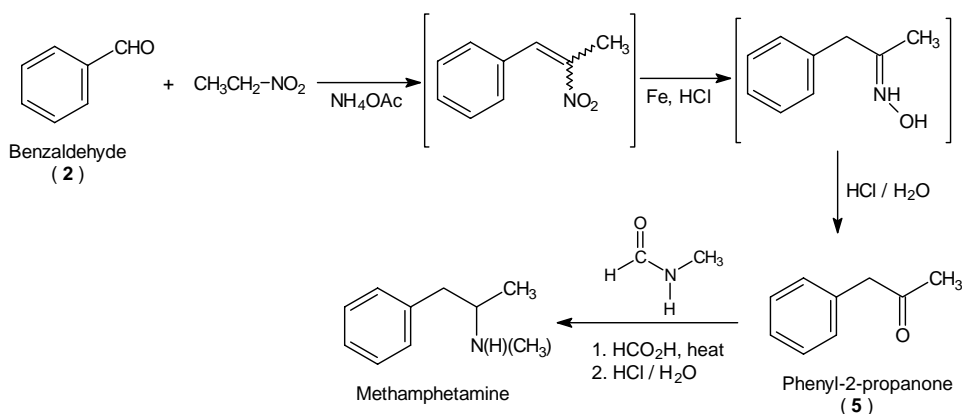


Fig. 5. Benzaldehyde (2) can be used as a starting material for the preparation of phenyl-2-propanone (P2P) (5), which is converted to methamphetamine using the Leukart method [9].

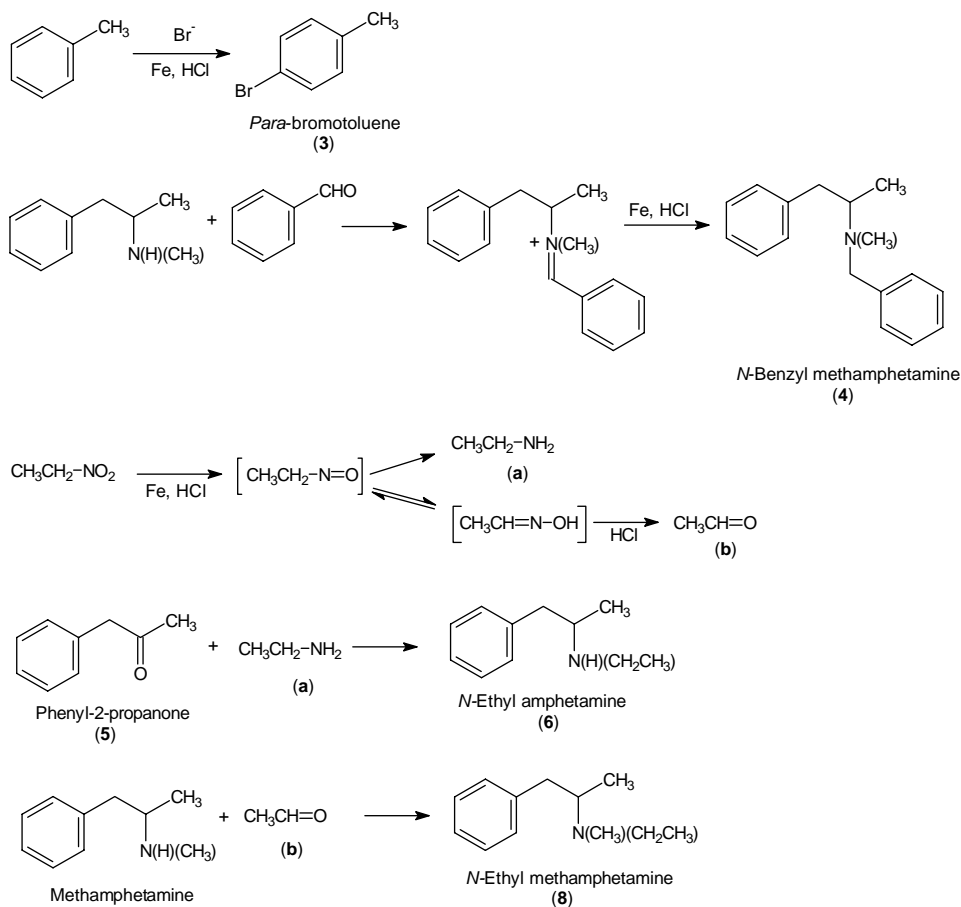


Fig. 6. Proposed mechanism to explain the presence of the newly identified impurities in the seized drug samples: *p*-bromotoluene (3); *N*-benzyl amphetamine (4); *N*-ethyl amphetamine (6); and *N*-ethyl methamphetamine (8) [9].

involved is a Leuckart synthesis. *N*-acetyl methamphetamine (10) may form as a byproduct during the precipitation of the free base methamphetamine by addition of hydrochloric acid in the presence of an acetate moiety, such as acetic acid, ammonium acetate or ethyl acetate solvent.

The proposed routes to the formation of the newly reported impurities are shown in Fig. 6. The use of toluene as a solvent, in the presence of iron and trace amounts of bromide during the Knoevenagel reaction between nitroethane and benzaldehyde, may lead to the formation of *p*-bromotoluene (3). *N*-Benzyl methamphetamine (4) and *N*-ethyl methamphetamine (8) may form from the reaction of methamphetamine with excess benzaldehyde and acetaldehyde, respectively. *N*-Ethyl amphetamine (6) may form from a side reaction between P2P and ethyl amine [9].

5. Conclusions

The result of the cluster analysis indicates there may be three big syndicates operating in the four areas of

Pangasinan, Zambales, Quezon Province, and Metro-Manila. The analysis of the impurities and the frequency of occurrence suggest that all three syndicates synthesize methamphetamine hydrochloride using the Leuckart method. The clustering observed probably reflects the differences in the laboratories and synthetic batches.

The accuracy of impurity profiling and clustering depends on the selection and quantification of an adequate number of impurity peaks in a sufficiently big collection of drug samples. In this study, we showed that for the set of 30 drug samples which were seized in the four areas, cluster analysis using 40 impurity peaks gave more consistent results than the use of 30 impurity peaks.

However, the following points should be emphasized. First, the minimum number of impurity peaks should be empirically determined since this depends on the number of impurities which are detected in all of drug samples available. Second, in the future, if illicit drug manufacturers use different methods, starting materials, or reaction conditions, other impurities may be introduced. Thus, it is recommended that impurities in drug samples be

continuously identified, quantified and added to the database. Cluster analysis should then be performed using an increasing number of impurity peaks until consistent clusters are obtained.

Finally, we wish to note that none of the casework samples contained ephedrine or pseudoephedrine, as well as the impurities associated with their use as starting material. From this, we can conclude that in the Philippines the synthesis or availability of methamphetamine starting from ephedrine or pseudoephedrine as starting material is not significant.

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