Identification of impurities and statistical classification of methamphetamine tablets (Ya-Ba) seized in Thailand

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Abstract

Impurity profiles of methamphetamine tablets seized in Thailand have been investigated. The samples are extracted with small amounts of ethyl acetate under alkaline condition and the extracts are analyzed by capillary gas chromatography. Nine compounds (1,2-dimethyl-3-phenylaziridine, ephedrine, methylephedrine, N-formylmethamphetamine, N-acetylmethamphetamine, N-formylephedrine, N-acetylephedrine, N,O-diacetylephedrie, methamphetamine dimer) are identified as impurities in methamphetamine tablet. Caffeine and ethyl vanillin are also detected as diluents and/or adulterants, and acetylcodeine monoacetylmorphine and diacetylmorphine are contained in many samples. In addition, trans-3,4-dimethyl-5-phenyl-2-oxazolidone is newly found as an impurity. For characterization and comparison of methamphetamine tablet exhibits, intensely and commonly detectable nine peaks are selected as the factor for multivariate analysis. The procedures reported here permit classification of 250 analyzed exhibits into five groups and characterization of classified groups. © 2002 Published by Elsevier Science Ireland Ltd.

Keywords: Methamphetamine tablet; Gas chromatography; Impurity; 3,4-Dimethyl-5-phenyl-2-oxazolidone; Hierarchical cluster analysis

1. Introduction

Southeast Asia sub-region has been suffered problems of production, trafficking and abuse of tablet form of methamphetamine called "Ya-Ba" over the past 10 years. Methamphetamine tablets have been mainly produced near the Thai/Myanmar border, and approximately 80% of the methamphetamine tablets in Thai market come from this source. Moreover, Thai authorities seized large amounts of methamphetamine tablets that were prepared to smuggle to many Asian and European countries.

Recently, the demand for an intimate knowledge of comparison of impurities contained in abused drugs has increased in forensic science field, as detailed impurity profiles can provide useful intelligence to law enforcement units concerning illicit drug production and trafficking. Several studies have been reported on impurity patterns and identification of impurities in Leuckart produced

methamphetamine [1–9]. In addition, some impurities in methamphetamine synthesized from ephedrine and comparison of impurity profiles have been reported [1,10–22].

Methamphetamine tablet usually consists of methamphetamine hydrochloride (20–30%), caffeine (60–70%) and others (starch, pigments and flavor compounds) and these diluents and adulterants make it difficult to implement direct comparison of impurity profile of methamphetamine itself.

In this paper, identification of impurities in methamphetamine tablets seized in Thailand and statistical approach for comparative analysis of methamphetamine exhibits are described.

2. Experimental

2.1. Apparatus

The gas chromatographic (GC) analysis was carried out on a Hewlett-Packard 5890 series II gas chromatograph

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equipped with a flame ionization detector. Injection of samples was made at the splitless mode using Hewlett-Packard 7673 autosampler. The column was a fused-silica capillary column, Ultra 2 (25 m × 0.2 mm i.d., film thickness 0.33 µm, Hewlett-Packard, USA). The injector and detector temperatures were maintained at 280 °C. The oven temperature was programmed as follows: initial temperature, 50 °C initial hold, 1 min; temperature program rate, 10 °C/min; final temperature, 300 °C final hold, 15 min. The carrier gas was helium at a flow rate of 1 ml/min. Data processing software (Entest Japan, Tokyo, Japan) was used for retention time compensation of gas chromatogram and peak integration.

^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra were recorded on a Bruker BZH-200 spectrometer in CDCl$_3$. Tetramethylsilane (TMS) was used as an internal standard.

Electron impact ionization (EI) mass spectra were obtained by using a Shimadzu QP-2000 gas chromatograph–mass spectrometer (GC–MS). Gas chromatographic conditions were the same as described above. The following conditions were used for mass spectrometry: ionization, EI mode; ionization current, 60 µA; ionization voltage, 70 eV. Chemical ionization (CI) mass spectra were measured by a Hewlett-Packard GC–MS. Gas chromatographic conditions were the same as described above. The following conditions were used for mass spectrometry: ionization, CI mode; ionization current, 250 µA; ionization voltage, 130 eV; reagent gas, methane.

2.2. Sample preparation

Methamphetamine tablet is usually orange color, but occasionally green, yellow, pink, red, brown colored tablets are present. Size of the tablet is about 6 mm of diameter and 3 mm of thickness. Average weight of one tablet is ca. 90 mg. Though the most popular logo marks are ''WY'' or ''Wy'', tablet with ''R'' or ''SY'' logos also present. Almost all seized methamphetamine package contains 200 of orange to red colored tablets and 2 green colored tablets. From the seized package of methamphetamine tablets, 20 tablets, which have same visual and physical characteristics, were taken. After the tablets were ground into powder, 100 mg of powdered sample was dissolved in 1 ml of 0.1 M phosphate buffer (pH 7.0). The solution was made basic with 0.25 ml of 10% Na$_2$CO$_3$, and extracted by vigorous shaking for 5 min with 0.4 ml of ethyl acetate containing triacontane (0.05 mg/ml) as an internal standard. After centrifugation, the organic layer was transferred into an insert of microvial (Hewlett-Packard) for the autosampler with a disposable pipette.

2.3. Preparation of standard compounds

2.3.1. Cis- and trans-1,2-dimethyl-3-phenylaziridine

Chloroephedrine hydrochloride (200 mg) was dissolved in 10% NaOH solution (2 ml) and refluxed for 2 h. After confirmation of the disappearance of the starting material by thin-layer chromatography (TLC, developing solvent: chloroform–methanol (95:5, v/v)), the reaction mixture was extracted three times with chloroform and organic solutions were combined, dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuo to give a mixture of cis- and trans-1,2-dimethyl-3-phenylaziridine.

Cl-MS (*m/z*): 148 (QM$^+$). El-MS (*m/z*): 146, 132, 117, 105, 91, 77, 65, 51 and 42.

2.3.2. N-formylmethamphetamine

To aqueous solution (5 ml) of methamphetamine hydrochloride (200 mg) and formic acid (98%, 0.1 ml), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (250 mg) was added. After stirring for 1.5 h at room temperature, the reaction mixture was extracted with ethyl acetate for three times under basic condition with 1 N NaOH solution. The organic solutions were combined, dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuo.

CI-MS (*m/z*) 178 (QM$^+$). El-MS (*m/z*): 118, 91, 86 and 58.

2.3.3. N-acetylmethamphetamine and N,O-diacetylephedrine

A solution of methamphetamine hydrochloride (100 mg) in dry pyridine (1 ml) and acetic anhydride (1 ml) was stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate, and the extract was washed with 1 N HCl solution and then 1 N NaOH solution. The organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuo to yield N-acetylmethamphetamine.

CI-MS (*m/z*): 192 (QM$^+$). El-MS (*m/z*): 100, 91, 77, 58 and 43.

N,O-diacetylephedrine was prepared by the same way described above, using ephedrine hydrochloride (100 mg) instead of methamphetamine hydrochloride.

Cl-MS (*m/z*): 250 (QM$^+$). El-MS (*m/z*): 100, 91, 77, 58 and 43.

2.3.4. N-formylephedrine

N-formylephedrine was prepared by the similar method for N-formylmethamphetamine described above.

CI-MS (*m/z*): 194 (QM$^+$). El-MS (*m/z*): 87, 86, 77, 72 and 58.

2.3.5. N-acetylephedrine

A total of 2 µl of perchloric acid (60%) was added to acetic anhydride (0.2 ml). The reagent solution was added to ephedrine free base (300 mg). After 30 min, the reaction mixture was extracted three times with chloroform and 1 N NaOH solution. The organic solutions were combined, dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuo.

CI-MS (*m/z*): 208 (QM$^+$). EI-MS (*m/z*): 101, 100, 77 and 58.

2.3.6. Cis-3,4-dimethyl-5-phenyl-2-oxazolidone

To a solution of ephedrine (200 mg) in benzene (10 ml), ethyl carbonate (160 mg) and sodium methoxide (75 mg)

were added. After stirring for 1.5 h at room temperature, the reaction mixture was washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated in vacuo.

^{1}H-NMR (δ): 0.70 (3H, d, $J = 6.5$ Hz), 2.79 (3H, s), 3.96 (1H, d-q, $J = 6.5$, 8.2 Hz), 5.50 (1H, d, $J = 8.2$ Hz) 7.16–7.31 (5H, m). ^{13}C-NMR (δ): 17.3, 28.7, 61.2, 82.4, 125.9, 128.8, 128.9, 137.6 and 157.8. CI-MS (*m/z*): 192 (QM$^+$). EI-MS (*m/z*): 191, 176, 147, 132, 117, 105, 91, 77, 57 and 43.

2.3.7. Trans-3,4-dimethyl-5-phenyl-2-oxazolidone

In a similar manner as described above, the reaction of *d*-pseudoephedirne (200 mg) with ethyl carbonate (160 mg) and sodium methoxide (75 mg) in benzene (10 ml) gave trans-3,4-dimethyl-5-phenyl-2-oxazolidone.

^{1}H-NMR (δ): 1.32 (3H, d, $J = 6.2$ Hz), 2.82 (3H, s), 3.50 (1H, d-q, $J = 6.2$, 7.8 Hz), 4.85 (1H, d, $J = 7.8$ Hz) 7.24–7.41 (5H, m). ^{13}C-NMR (δ): 14.2, 28.9, 56.9, 78.3, 126.1, 127.9, 128.4, 135.1 and 158.1. CI-MS (*m/z*): 192 (QM$^+$). EI-MS (*m/z*) 191, 176, 147, 132, 117, 105, 91, 77, 57 and 43.

2.4. Data analysis

For hierarchical cluster analysis (HCA), six identified compounds (ephedrine, *N*-formylmethamphetamine, *N*-acetylmethamphetamine, *trans*-3,4-dimethyl-5-phenyl-2-oxazolidone, *N*-acetylephedrine, methamphetamine dimer) and three unidentified compounds found as impurities in methamphetamine tablet were used as the factors. Their peak area ratios to the internal standard were calculated to give a data matrix. Selection of these peaks in each chromatogram, calculation of their peak area ratio were automatically performed with the data processing software (Entest Japan). HCA was done on the matrix with a Windows 98 software Pirouette (Infometrix Co., Woodinville, WA, USA) and incremental linkage method was used. Similarity index value were calculated by following equation; similarity$_{a,b} = 1 - d_{a,b}/d_{max}$ ($d_{a,b}$ is the Euclidian distance of sample a and b, and d_{max} the largest Euclidian distance in the data set).

3. Results and discussion

3.1. Identification of impurities

As preliminary experiments we performed GC analysis using one methamphetamine tablet per one sample preparation. The tablets having similar visual and physical characteristics in the same package showed very similar gas chromatograms. From these facts 20 similar tablets in the same package were used for extraction as described in Section 2.

Typical gas chromatograms of the ethyl acetate extracts of methamphetamine tablets are shown in Fig. 1. Peaks 2, 5 and 13 were confirmed to be methamphetamine, ethyl vanillin and caffeine by GC–MS, respectively, Fig. 2 shows gas

chromatograms of the ethyl acetate extracts of crystals of methamphetamine hydrochloride seized in Thailand. As peak 1 and the peaks detected in regions I and II in Fig. 1 were also observed in Fig. 2, these peaks were assumed to originate from impurities contained in methamphetamine preparation.

Fig. 3 shows EI mass spectra of peaks 1, 3, 4, 6, 7, 8, 10, 11, 12, 14, 15 and 16 in Fig. 1. From the comparative analysis of respective peak retention time and mass spectral data with those of authentic and synthesized compounds, peaks 1, 3, 4, 7, 8, 10, 11 and 12 were identified to be 1,2-dimethyl-3-phenylaziridine, ephedrine, methylephedrine, *N*-formylmethamphetamine, *N*-acetylmethamphetamine, *N*-formylephedrine, *N*-acetylephedrine and *N,O*-diacetyle-phedrine, respectively (Fig. 3).

In mass spectrum of peak 14 (Fig. 3j), intense fragment ion peaks were observed at *m/z* 238, 148, 120, 91 and 58. This mass spectrum was similar with those of methamphetamine dimer and *N*-methyl-*N*-(α-methylphenethyl)amino-l-phenyl-2-propanone. However, it is reported that the latter compound gives relatively strong fragment ions at *m/z* 190, 133 and 105 [22]. By comparison of mass spectral data [22], peak 14 was assumed to be methamphetamine dimer.

Presence of 1,2-dimethyl-3-phenylaziridine and ephedrine in almost all Ya-Ba tablets indicated that methamphetamine in those samples was mainly prepared from ephedrine. However, ephedrine and pseudoephedrine could not be separated under the GC conditions used in this study. Detailed identification of the precursor is under investigation.

Cantrell et al. [15] and Skinner [19] have reported phenyl-2-propanone (P2P), *cis*- and *trans*-1,2-dimethyl-3-phenyla-ziridine, 1-benzyl-3-methylnaphthalene and l,3-dimethyl-2-phenylnaphthalene as impurities in methamphetamine synthesized by hydriodic acid/red phosphorous method. However, P2P and naphthalene type compounds were not detected in this study. On the other hand, it is well known that chloroephedrine easily converts to l,2-dimethyl-3-phenyl-aziridine during GC analysis. In addition, huge amounts of thionyl chloride are seized from clandestine laboratories around the Thai/Myanmar border. Therefore, Emde method is the most possible procedure of illegal methamphetamine production in this sub-region.

Fig. 4 shows EI mass spectrum of peak 9 (compound X) in Fig. 1. A molecular ion (M^+) was observed at *m/z* 191 and fragment ions were observed at *m/z* 176, 147, 131, 117, 105, 91, 77, 57 and 42 (base peak). Beckett et al. [23] studied about the degradation of ephedrine and identified 2,3,4-trimethyl-5-phenyloxazolidine as one of the decomposed compounds. The molecular weight of compound X was coincident with that of 2,3,4-trimethyl-5-phenyloxazolidine and also with those of 3,4-dimethyl-2-phenylmorpholine and 3,4-dimethyl-5-phenyl-2-oxazolidone. However, the characteristic fragment ion (*m/z* 85, given by cleavage of benzaldehyde in 2,3,4-trimethyl-5-phenyloxazolidine and 3,4-dimethyl-2-phenylmorpholine) was not observed in
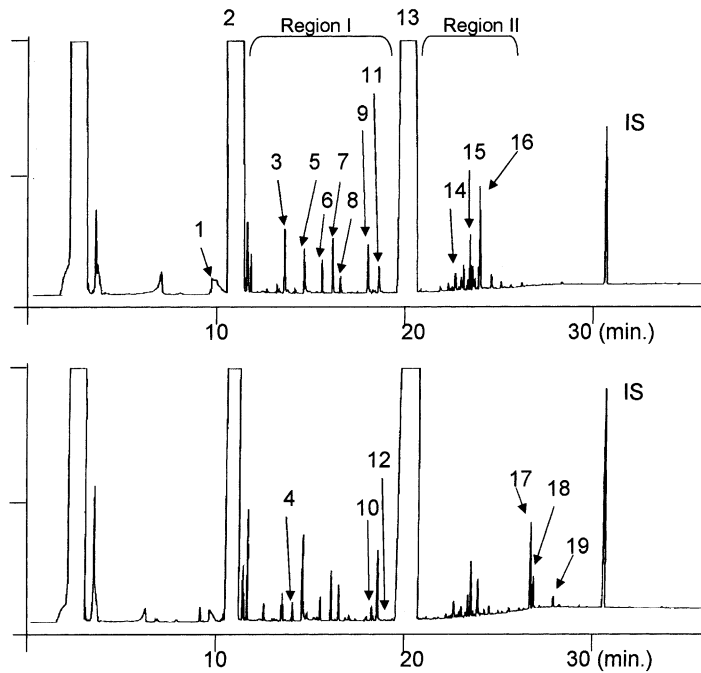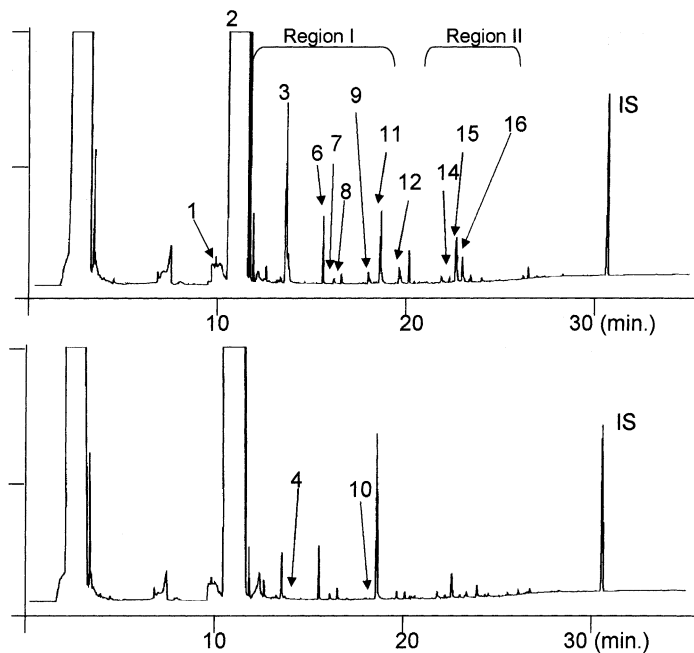
Fig. 1. Gas chromatograms of the extracts of methamphetamine tablets. 1,1,2-Dimethyl-3-phenylaziridine; 2, methamphetamine; 3, ephedrine; 4, methylephedrine; 5, ethyl vanillin; 6, unidentified-1; 7, *N*-formylmethamphetamine; 8, *N*-acetylmethamphetamine; 9, *trans*-3,4-dimetyl-5-phenyl-2-oxazolidone; 10, *N*-formylephedrine; 11, aacetylephedrine; 12, *N,O*-diacetylephedrine; 13, caffeine; 14, methamphetamine dimer; 15, unidentified-2; 16, unidentified-3; 17, acetylcodeine; 18, monoacetylmorphine; 19, diacetylmorphine (heroin).

Fig. 2. Gas chromatograms of the extracts of methamphetamine crystal. 1,1,2-Dimethyl-3-phenylazlridine; 2, methamphetamine; 3, ephedrine; 4, methylephedrine; 6, unidentified-1; 7, *N*-formylmethamphetamine; 8, *N*-acetylmethamphetamine; 9, *trans*-3,4-dimetyl-5-phenyl-2-oxazolidone; 10, *N*-formylephedrine; 11,*N*-acetylephedrine; 12, *N,O*-diacetylephedrine; 14, methamphetamine dimer; 15, unidentified-2; 16, unidentified-3; 17, acetylcodeine; 18, monoacetylmorphine; 19, diacetylmorphine (heroin).
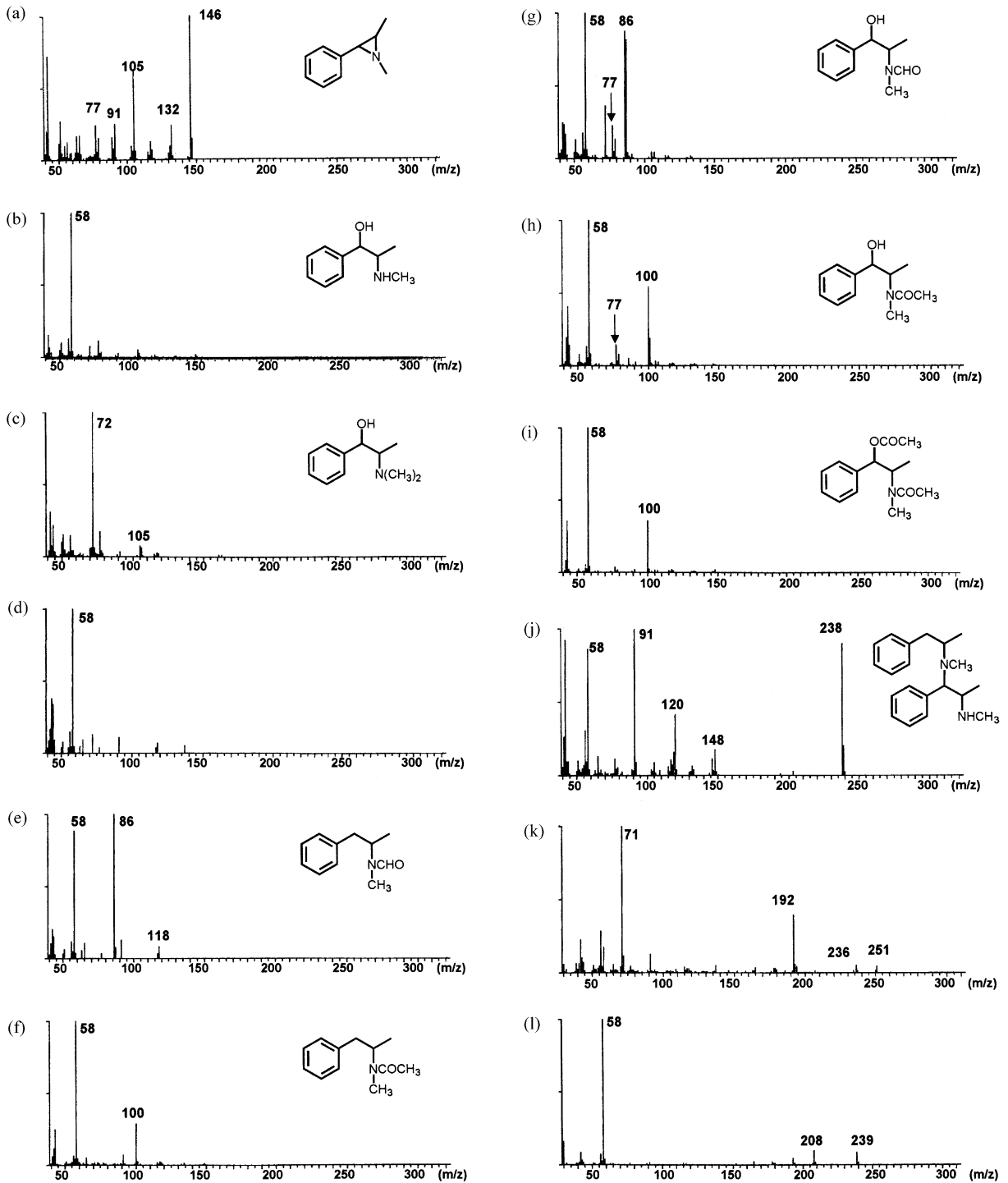
Fig. 3. El mass spectra of the peaks in Fig. 1. (a) Peak 1 (1,2-dimethyl-3-phenylaziridine); (b) peak 3 (ephedrine); (c) peak 4 (methylephedrine); (d), peak 6 (unidentified-1); (e) peak 7 (N-formylmethamphetamine); (f) peak 8 (N-acetylmethamphetamine); (g) peak 10 (N-formylephedrine); (h) peak 11 (N-acetylephedrine); (i) peak 12 (N,O-diacetylephedrine); (j) peak 14 (methamphetamine dimer); (k) peak 15 (unidentified-2); (l) peak 16 (unidentified-3).
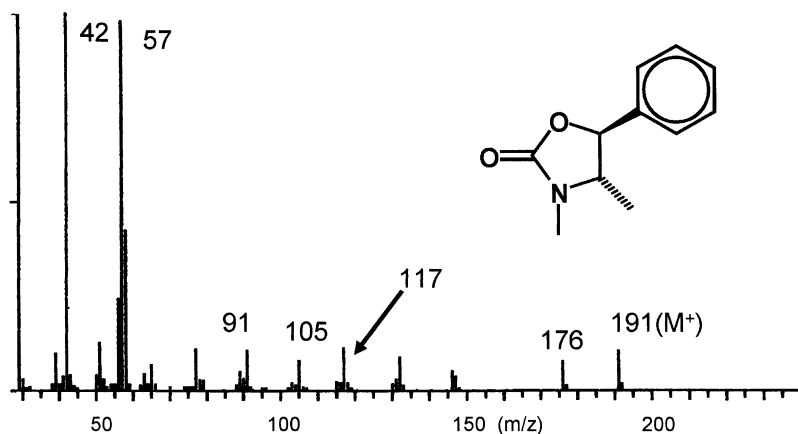
Fig. 4. Mass spectrum of peak 9 in Fig. 1.

the mass spectrum of the compound X (Fig. 4), and thus, the compound X seemed to be 3,4-dimethyl-5-phenyl-2-oxazolidone.

For the structure elucidation of this compound, two isomer, *cis*- and *trans*-3,4-dimethyl-5-phenyl-2-oxazolidone, were prepared from ephedrine and pseudoephedrine, respectively [24]. On GC and GC–MS analysis, the retention time of the compound X was consistent with that of *trans*-3,4-dimethyl-5-phenyl-2-oxazolidone and mass spectra of both compounds were coincident completely. It is notable that the configuration of the oxazolidone is the same with pseudoephedrine, and process to generate this compound is under investigation.

In addition, GC–MS revealed that many Ya-Ba tablets contained very small amount of acetylcodeine, monoacetylmorphine and diacetylmorphine (heroin) as shown in Fig. 1. There is considerable difficulty in estimating the reason of presence of these compounds. The areas of methamphetamine clandestine laboratories locate in this sub-region overlap with those of illicit opium poppy and heroin production. Methamphetamine preparation might be contaminated with the trace amounts of these compounds at some refineries, which produced both methamphetamine and heroin.

Identification of other impurities found on the gas chromatogram is under investigation. The impurities identified in Ya-Ba tablets here were summarized in Fig. 5.
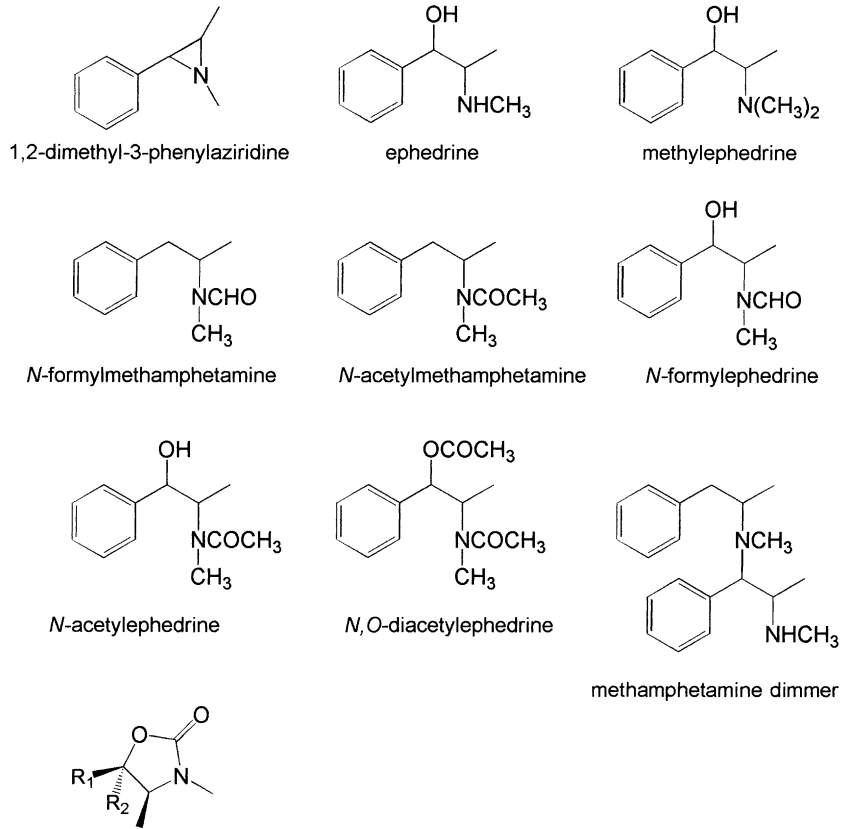
Remberg et al. [22] have reported 26 compounds as impurities found in seized methamphetamine samples, and described about the presence of benzaldehyde, *cis*-1, 2-dimethyl-3-phenylaziridine, amphetamine, 3,4-dimethyl-5-phenyloxazolidine, ethyl vanillin, methylephedrine, *N*-formylmethamphetamine, *N*-acetylmethamphetamine, *N*-acetylephedrine and methamphetamine dimer as impurities in methamphetamine tablet. In this study, however, benzaldehyde, amphetamine and 3,4-dimethyl-5-phenyloxazolidine were not detected by GC–MS, and to our knowledge, it is the

first report of the presence of *trans*-3,4-dimethyl-5-phenyl-2-oxazolidone in methamphetamine preparation.

3.2. Comparison of Ya-Ba tablets by multivariate analysis

For the final decision on comparison of Ya-Ba tablets, the visual critical inspection of the chromatograms with all other available data such as physical characteristics of the tablets must be performed. However, the application of modern multidimensional statistical methods should be a very good approach for a group classification of complex chromatograms with numerous components in large data sets.

Intensely and commonly detected 9 peaks (ephedrine (peak 3 in Fig. 1), unidentified peak 1 (UN-1, peak 6), *N*-formylmethamphetamine (peak 7), *N*-acetylmethamphetamine (peak 8), *trans*-3,4-dimethyl-5-phenyl-2-oxazolidone (peak 9), *N*-acetylephedrine (peak 11), methamphetamine dimer (peak 14), unidentified peaks 2 (UN-2, peak 15) and 3 (UN-3, peak 16)) were selected as factors for multivariate analysis. Relative intensities of respective peaks to internal standard were calculated for 250 samples and the data matrix obtained was examined by HCA. The resultant dendrogram shown in Fig. 6 were useful to get a pre-selection of profiles of high similarity. The data set was classified into five groups at the level of similarity index value 0.55 and representative chromatograms for those groups are shown in Fig. 7. *Trans*-3,4-dimethyl-5-phenyl-2-oxazolidone, methamphetamine dimer and UN-3 in group 1, UN-2 and UN-3 in group 2, ephedrine and *N*-acetylephedrine in group 3, UN-3, UN-2 and ephedrine in group 4 and *N*-formylmethamphetamine ephedrine and UN-2 in group 5 were found as major impurities in each group (Fig. 7). Though more comprehensive sampling with more information of sample origin would be needed, these results suggested that the nine peaks selected in this study should be the good indicator to classify Ya-Ba tablets.

Fig. 5. Chemical structures of impurities found in Ya-Ba tablets.

1,2-dimethyl-3-phenylaziridine

ephedrine

methylephedrine

N-formylmethamphetamine

N-acetylmethamphetamine

N-formylephedrine

N-acetylephedrine

N,O-diacetylephedrine

methamphetamine dimmer

cis-3,4-dimethyl-5-phenyl-2-oxazolidone: $R_1=C_6H_5$, $R_2=H$
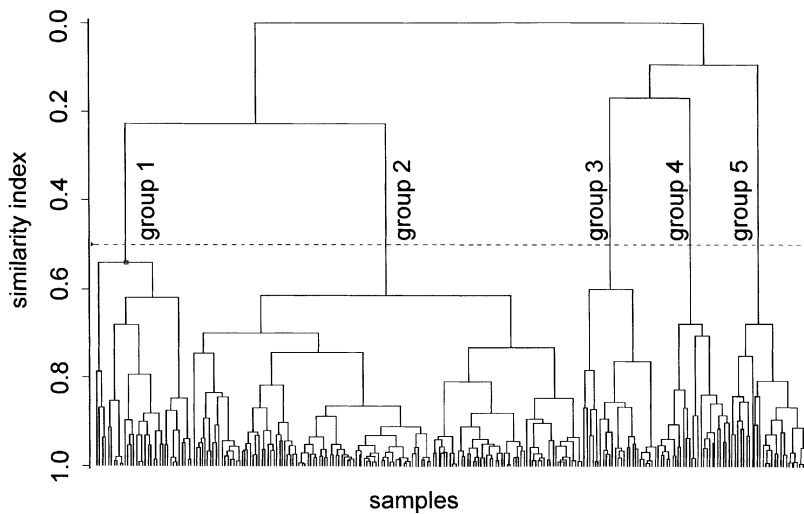*trans*-3,4-dimethyl-5-phenyl-2-oxazolidone: $R_1=H$, $R_2=C_6H_5$

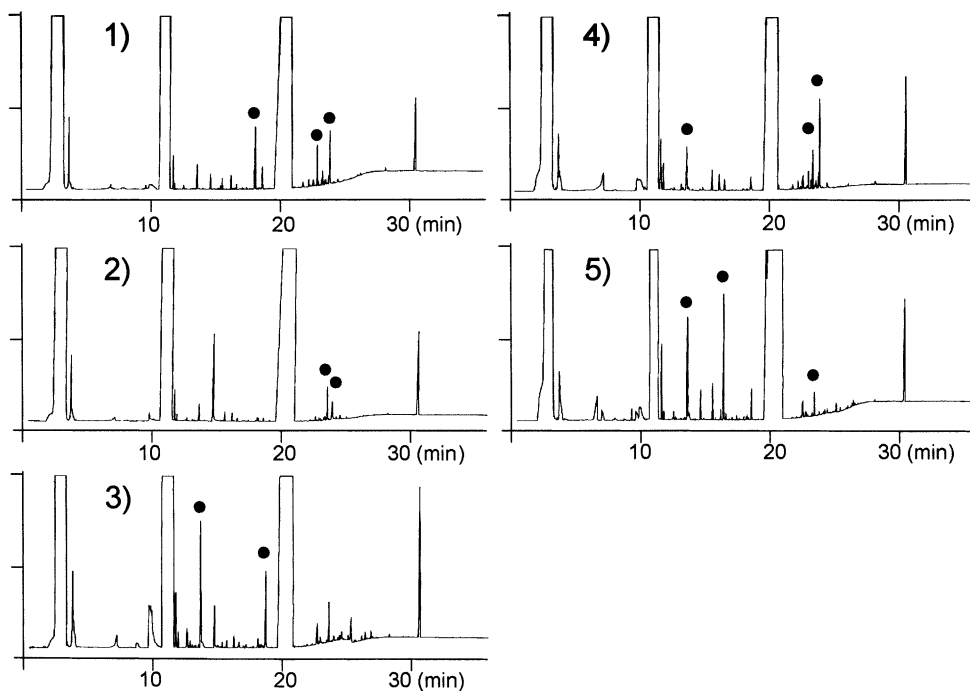Fig. 6. Dendrogram resulting from hierarchical cluster analysis of methamphetamine tablets.

Fig. 7. Typical gas chromatograms of methamphetamine groups classified by cluster analysis: (1) group in Fig. 5; (2) group 2 in Fig. 5; (3) group 3 in Fig. 5; (4) group 4 in Fig. 5; (5) group 5 in Fig. 5. Points in chromatograms indicate the characteristic peaks in each group.

4. Conclusion

Impurity profiles of methamphetamine tablets seized in Thailand have been investigated. 1,2-Dimethyl-3-phenyla-ziridine, ephedrine, methylephedrine, N-formylmethamphe-tamine, N-acetylmethamphetamine, N-formylephedrine, N-acetylephedrine, N,O-diacetylephedrine, methamphetamine dimer were confirmed as impurities with caffeine and ethyl vanillin as diluents and/or adulterants. Acetylcodeine, monoacetylmorphine and diacetylmorphine were also detected in many samples. In addition, the presence of a hitherto unreported impurity was revealed and it was identified as *trans*-3,4-dimethyl-5-phenyl-2-oxazolidone by synthesis and GC–MS. Furthermore, HCA using peak area ratios of intensely and commonly detectable nine impurities to the internal standard as variables proved to be a very valuable tool for comparison and characterization of illicit methamphetamine tablets.

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