ANALYSIS OF IMPURITIES IN ILLICIT METHAMPHETAMINE

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Summary

Impurity profiles of methamphetamine samples seized in Japan have been investigated. The samples are extracted with small amounts of hexane under alkaline conditions and the extracts are analyzed by gas chromatography (GC). Several impurity peaks are found in each chromatogram and the comparison of impurity profiles permits the establishment of common or different origins of methamphetamine seizures. The presence of ephedrine, which is a starting material for illegal methamphetamine preparations, is confirmed in all samples. In addition, methamphetamine dimer is newly found as an impurity and its structure is elucidated by the comparison of its retention time on GC and its mass spectrum with that of the authentic compound synthesized by condensation of cis-1,2-dimethyl-3-phenyl aziridine and (+)-methamphetamine.

Key words: Methamphetamine; Impurities; Ephedrine; Gas chromatography; Methamphetamine dimer

Introduction

Methamphetamine is one of the most popular abused drugs in Japan. It has been reported that the seized methamphetamine samples contain traces of starting materials and/or by-products of the reactions as their impurities [1–18].

Recently, the demand for an intimate knowledge of the composition of these impurities has increased in the forensic science field, as detailed impurity profiles can provide valuable information concerning illegal methods of manufacture. In addition, the comparison of such impurity profiles can aid in identifying the common origin of drug samples.

In 1983, Strömberg reported a gas chromatographic method for the display of impurity profiles of Leuckart-synthesized methamphetamine and pointed out that the method permitted the establishment of common or different origins of methamphetamine seizures [13].
Kram et al. identified $\alpha$-benzyl-$N$-methylphenethylamine, $N,N$-di($\beta$-phenethylisopropyl)amine, $N,N$-di($\beta$-phenethylisopropyl)methylamine and nine other compounds as impurities in methamphetamine synthesized by the Leuckart reaction [5] and Kishi et al. reported 1,2-dimethyl-3-phenyl aziridine, 1-phenyl-2-methyl-4-amino-1-propanone, ephedrine and 1-chloro-1-phenyl-2-methylaminopropane (chloroephedrine) as impurities in methamphetamine synthesized from ephedrine [12]. Furthermore, Cantrell et al. [14] and Skinner [18] elucidated the structures of two impurities, 1-benzyl-3-methylnaphthalene and 1,3-dimethyl-2-phenynaphtalene, in methamphetamine synthesized from ephedrine via reduction with hydroiodic acid.

In the present studies, the structure of a newly found impurity in illicit methamphetamine samples seized in Japan, is identified and a gas chromatographic analytical method for impurities in methamphetamine preparations, which seem to be prepared from ephedrine, is described.

**Experimental**

**Apparatus**

The gas chromatographic analysis was carried out on a Shimadzu GC-15A gas chromatograph equipped with a flame ionization detector. The column was a fused-silica wide-bore capillary column, DB-1 (15 m × 0.53 mm i.d., film thickness 1.5 $\mu$m, J & W, CA, USA). The oven temperature was programmed as follows: 110°C for 1 min, 15°C/min to 200°C, 2°C/min to 208°C, 10°C/min to 300°C and then 300°C for 10 min. The injector and detector temperatures were 250°C and 270°C, respectively. The helium carrier gas flow-rate was 10 ml/min and the injection port was the splitless mode.

$^1$H- and $^{13}$C-nuclear magnetic resonance (NMR) spectra were recorded on a Valian VXR-300 spectrometer in CDCl$_3$ and CD$_3$OD. Tetramethyilsilane (TMS) was used as an internal standard.

Gas chromatography-mass spectrometry (GC-MS) was performed on a JEOL SX-102 gas chromatograph-mass spectrometer. Gas chromatographic conditions were the same as described above. The following conditions were used for mass spectrometry: ionization, chemical ionization (CI) mode; ionization current, 300 $\mu$A; ionization voltage, 200 eV; reagent gas, isobutane.

Melting points were determined on a Kofler-type apparatus and uncorrected.

**Sample extraction**

A sample (200 mg) of seized methamphetamine sample was dissolved in 2 ml of 0.1 M phosphate buffer (pH 7.0). The solution was alkalized with 0.5 ml of 10% Na$_2$CO$_3$ and extracted by shaking for 10 min with 0.2 ml of n-hexane, containing tetratriacontane (0.1 mg/ml) as internal standard. After centrifugation the organic layer (top) was transferred to a small glass tube with a disposable pipette and 4 $\mu$l of the extract was injected into a GC or GC-MS.
Synthesis

Cis- and trans-1,2-dimethyl-3-phenyl aziridine

Chloroephedrine hydrochloride (200 mg), which was prepared from (−)-ephedrine and thionyl chloride [19], 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 the organic solutions were combined, dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuo. The residue was purified by preparative-TLC (developing solvent: chloroform-methanol (95:5, v/v)) and 100 mg of cis-aziridine and 10 mg of trans-aziridine were obtained. Their identity was confirmed by $^1$H-NMR [20] and CI-MS spectra.

Cis-1,2-dimethyl-3-phenyl aziridine. $^1$H-NMR (δ): 0.91 (3H, d, $J = 6$ Hz), 1.67 (1H, m, $J = 6$ Hz), 2.43 (1H, d, $J = 6$ Hz), 2.48 (3H, s), 7.15 – 7.35 (5H, m). CI-MS (m/z): 148 (QM$^+$).

Trans-1,2-dimethyl-3-phenyl aziridine. $^1$H-NMR (δ): 1.34 (3H, d, $J = 6$ Hz), 2.02 – 2.13 (2H, m), 3.55 (3H, s), 7.15 – 7.35 (5H, m). CI-MS (m/z): 148 (QM$^+$).

Compound 1

Anhydrous aluminum trichloride (136 mg) was added to a benzene solution (10 ml) of cis-aziridine (100 mg) and (+)-methamphetamine (201 mg). The reaction mixture was heated under reflux for 6 h. After cooling, the mixture was alkalinized with 10 N KOH solution and extracted three times with ethyl acetate and the organic solutions were combined, dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuo. The residue was purified by preparative-TLC (developing solvent: chloroform-methanol (95:5, v/v)) and compound 1 was isolated as a major product. The hydrochloride of the product was prepared in the usual way and the salt was recrystallized from methanol-ether solution.

Compound 1. m.p. (hydrochloride): 149 – 153°C. $^1$H-NMR (δ): 0.60 (3H, d, $J = 6.4$ Hz), 0.74 (3H, d, $J = 6.2$ Hz), 2.19 (3H, s), 2.33 (3H, s), 2.34 (1H, dd, $J = 6.9$, 13.1 Hz), 2.56 (1H, dd, $J = 6.4$, 13.1 Hz), 2.86 (1H, dd, $J = 6.2$, 9.6 Hz), 3.06 (1H, m), 3.40 (1H, d, $J = 9.6$ Hz), 7.08 – 7.34 (10H, m). $^{13}$C-NMR (δ): 16.3, 16.5, 32.2, 34.2, 41.2, 54.3, 56.9, 73.6, 125.8, 127.0, 128.0, 128.1, 129.2, 129.3, 138.3, 140.8. CI-MS (m/z): 297 (QM$^+$), 238, 150, 148.

Compound 2

Anhydrous aluminum trichloride (540 mg) was added to a benzene solution of trans-aziridine (200 mg) and (+)-methamphetamine (400 mg). The reaction mixture was refluxed for 3 h. After cooling, the reaction mixture was alkalinized with 10 N KOH solution and extracted three times with ethyl acetate. The organic solutions were combined, dried over anhydrous Na$_2$SO$_4$ and evaporated in vacuo. The product (compound 2) was isolated by repeated preparative-TLC using two developing solvent systems (chloroform saturated with ammonia and chloroform-methanol (90:10, v/v)). The hydrochloride of the product was
prepared in the usual way and the salt was recrystallized from methanol-ether solution.

**Compound 2.** m.p. (hydrochloride): 193–197°C. $^1$H-NMR (δ): 0.81 (3H, d, $J = 6.3$ Hz), 0.87 (3H, d, $J = 6.2$ Hz), 2.19 (3H, s), 2.26 (3H, s), 2.40 (1H, dd, $J = 7.2, 13.5$ Hz), 2.79 (1H, dd, $J = 6.6, 13.5$ Hz), 2.98–3.08 (2H, m), 3.44 (1H, d, $J = 6.3$ Hz), 7.08–7.34 (10H, m). $^{13}$C-NMR (δ): 15.3, 16.5, 31.5, 34.1, 39.2, 55.2, 57.4, 72.2, 125.8, 127.3, 128.1, 129.1, 129.5, 138.5, 140.8. CI-MS (m/z): 297 (QM$^+$), 238, 150, 148.

**Results and Discussion**

**GC and GC-MS analysis of seized methamphetamine**

Fifty-nine methamphetamine samples seized at ten different places in Japan were analyzed by GC and GC-MS.

Some typical gas chromatograms of extracts are shown in Fig. 1. Although Strömberg et al. [13] and Allen et al. [15] used the acidic extraction for analysis of impurities in methamphetamine, the acidic extract of methamphetamine seized in Japan showed no GC peaks.

Peak 1 and 2, indicating the same retention times as methamphetamine and ephedrine, were confirmed to be methamphetamine (peak 1) and ephedrine (peak

![Fig. 1. Gas chromatograms of extracts of methamphetamine seizures. Peak 1, methamphetamine; peak 2, ephedrine; peak 3, compound 1.](image-url)
2) by GC-MS analysis, respectively. The peak of ephedrine was found in all methamphetamine samples analyzed here. Kishi et al. also reported that ephedrine was detected in 11 of 14 methamphetamine samples seized in Japan [12] and it is well known that methamphetamine abused in Japan is the (+)-isomer. These facts indicates that the methamphetamine abused in Japan is prepared from ephedrine.

Peaks detected in region I (retention time 10–18 min) were assumed to originate from impurities contained in methamphetamine preparations, as these peaks were not observed in the blank extract. These impurity profiles of methamphetamine prepared from ephedrine are simpler relative to those of methamphetamine synthesized from benzyl methyl ketone by the Leuckart reaction [13,17]. However, the peak patterns in this region were different from sample

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cis -aziridine

\[ \text{trans -aziridine} \]
to sample depending on place of seizure. The comparison of these impurity profiles will permit the establishment of a common origin for the samples, since the reproducible preparation of methamphetaminne in a clandestine laboratory is very difficult, thereby causing a great inter-batch variation in evidential drug samples.

**Structure of major impurity (compound X)**

Figure 2 shows the CI-mass spectrum of peak 3, which is the common and relatively intense peak in region I of Fig. 1 and the impurity giving this peak 3 is tentatively named as compound X. A quasi-molecular ion (QM+) was observed at \( m/z \) 297 and diagnostic fragment ion peaks were detected at \( m/z \) 150 (base peak) and 238. The molecular weight of this compound \( (MW: 296) \) coincided with double the weight of deprotonated methamphetamine \( (MW: 148) \). The presence of the fragment ion at \( m/z \) 238 \( (QM^+ - 59) \) indicated that compound X had the \( CH_3CH-NHCH_3 \) grouping in its structure.

These results showed that the compound X might be a dimer of methamphetamine and that a carbon atom at the benzylic position of one methamphetamine moiety might be bound to a nitrogen atom of another methamphetamine moiety.

Kishi et al. found 1,2-dimethyl-3-phenyl aziridine in methamphetamine samples synthesized from ephedrine [12]. Recently, Cantrell et al. reported a hypothesis about the aziridine formation in methamphetamine preparations from ephedrine with hydroiodic acid and phosphorus [16]. Thus, in the course of the illegal

![Proton-proton shift correlation spectrum of compound 1.](image-url)
preparation of methamphetamine, the compound X seems to be formed by the condensation of 1,2-dimethyl-3-phenyl aziridine and methamphetamine.

It is well known that there are two stereoisomers in 1,2-dimethyl-3-phenyl aziridine, cis- and trans-aziridine [15,20,21]. Consequently, the configuration of the benzyllic carbon of aziridine will decide the configuration of compound X at the benzylcine methane carbon adjacent to the amino group.

For the structural elucidation of compound X, two dimers, compound 1 and 2, were synthesized by the condensation of cis- or trans-aziridine with (+)-methamphetamine (Scheme 1).

Confirmation of the structure of the synthesized compounds was performed by mass spectral analysis and 2D-NMR experiments.

In CI-mass spectra, both synthesized compounds showed a similar mass spectrum with a QM* at m/z 297. The result of 1H-1H shift correlation spectroscopy (COSY) experiments [22] of compound 1 is shown in Fig. 3. Signal I (δH 2.86), the methine proton (proton e) adjacent to an amino grouping, coupled with the methyl proton (proton f, δH 0.74) and the benzylcine methane proton (proton d, δH 3.40) adjacent to an amino grouping. Signal II (δH 3.06), the methine proton (proton b) adjacent to an amino grouping, coupled with the methyl protons (proton c, δH 0.60) and the benzylcine methylene protons (proton a and a’, δH 2.34 and 2.56). While compound 2 synthesized from the trans-aziridine showed the signal at δH 2.98 – 3.08 (methine proton adjacent to an amino grouping) coupling with the methyl protons (δH 0.81) and the benzylcine methane proton adjacent to an amino grouping (δH 3.44) and the signal at δH 2.98 – 3.08 (methine proton adjacent to an amino grouping) coupling with the methyl protons (δH 0.87) and the benzilic methylene protons (δH 2.40 and 2.79). These spectral data indicate that the structures of both synthesized compounds are formula 1 and 2 in Scheme 1, respectively.

On GC and GC-MS analysis, the retention time of compound X contained in seized methamphetamine was consistent with that of the authentic sample prepared from the cis-aziridine and (+)-methamphetamine and mass spectra of both compounds coincided completely. From these results, the structure of compound X seems to be represented by formula 1.

It seems reasonable that such a methamphetamine dimer is found as an impurity and that the amount of the dimer originating from the cis-aziridine is larger than that from the trans-aziridine, because ephedrine can easily convert to aziridine under acidic conditions and the cis-isomer is more stable than the trans-isomer.

Identification of other impurities found on the gas chromatogram in this study is under investigation.

Conclusion

Impurity profiles of methamphetamine samples seized in Japan have been investigated, primarily aimed at establishing the common or different origin of the samples. Ephedrine, a starting material for illegal methamphetamine preparations, has been confirmed in all samples. In addition, a methamphetamine dimer
was found as an impurity and its structure was elucidated by the comparison of its retention time on GC and its mass spectrum with that of the authentic compound which was synthesized by condensation of cis-1,2-dimethyl-3-phenyl aziridine and (+)-methamphetamine.

Gas chromatographic profiles of the basic extract from illicit methamphetamine have proved to be efficiently applicable to the establishment of a common or different origin for methamphetamine seizures.

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References


