Recently, some pharmaceutical companies have changed the manufacturing process of semisynthetic ephedrines for medical use; commercial semisynthetic ephedrines are now produced from molasses and from pyruvic acid [7,8]. The $\delta^{13}C$ value of semisynthetic ephedrines derived from pyruvic acid was similar to that of synthetic or biosynthetic ephedrines. Therefore, clear-cut classification cannot be achieved only from $\delta^{13}C$ and $\delta^{15}N$ values. We anticipated that hydrogen isotope ratio analysis would likely be a powerful tool for identification of the origin of ephedrines. In general, hydrogen isotope patterns can be determined by ^2H NMR or isotope ratio mass spectrometry (IR-MS) [9–14]. We selected IR-MS, because it requires only about 10 min per measurement, while ^2H NMR takes about 8 h per measurement. A short measurement time is advantageous for forensic work. Here, we demonstrate the utility of hydrogen stable isotope ratio, in combination with $\delta^{13}C$ and $\delta^{15}N$ values, determined by IR-MS for the discrimination of the origin of ephedrines used as a precursor of seized methamphetamine.

2. Materials and methods

2.1. Ephedrine and methamphetamine samples

The samples were as follows: sixteen *l*-ephedrine/HCl, 10 *d*-pseudoephedrine/HCl and one *d*-pseudoephedrine/$(H_2SO_4)_{1/2}$ (shown in Table 1). There are two kinds of commercial semisynthetic ephedrines, one produced from molasses and the other from pyruvic acid. Seven methamphetamine/HCl samples were synthesized from the ephedrines by the Nagai or Emde method, as shown in Fig. 1. Two *l*-ephedrine/HCl samples seized in Myanmar, and 25 samples of illicit methamphetamine/HCl seized in Japan were also used.

2.2. Instruments

2.2.1. IR-MS system for carbon and nitrogen isotope ratio analysis

A stable isotope ratio mass spectrometer Delta^{Plus} (ThermoFinnigan, USA) equipped with an elemental analyzer, Flash EA1112 (ThermoFinnigan, USA), was used for the measurements of carbon and nitrogen isotope ratios of samples. Individual samples (300 μg) wrapped in tin foil were flash-combusted in an elemental analyzer to afford CO_2, NO_x and H_2O in an O_2 atmosphere in a quartz reactor packed with Cr_2O_3 on alumina and Co_3O_4/Ag. The gases were passed through a copper reactor to reduce NO_x to N_2. H_2O was trapped with $Mg(ClO_4)_2$. Then CO_2 and N_2 were separated on a GC column, and subjected to IR-MS to obtain the $^{13}C/^{12}C$ and $^{15}N/^{14}N$ ratios. The stable isotope ratios are expressed relative to the conventional standards, i.e., Peedee Belemite for carbon and atmospheric N_2 for nitrogen. The δ values were defined according to the following equation:

$$\delta^{13}C \text{ or } ^{15}N\,(‰) = \left[\frac{R_{sample}}{R_{standard}} - 1\right] \times 1000,$$

where $R = {}^{13}C/{}^{12}C$ or $^{15}N/^{14}N$. Each sample was measured five times. We checked the analytical stability daily by acquiring data from a known laboratory isotopic standard. Sample values were corrected based on the value of the laboratory isotopic standard. The repeatabilities routinely obtained were 0.1‰ or less for $\delta^{13}C$ and 0.2‰ or less for $\delta^{15}N$.

2.2.2. IR-MS system for hydrogen isotope ratio analysis

A stable isotope ratio mass spectrometer Delta V (Thermo Electron, USA) equipped with a high temperature conversion elemental analyzer TC/EA (Thermo Electron, USA) was used for the measurements of hydrogen isotope ratios of samples. Individual samples (245 μg for ephedrines and 230 μg for methamphetamine) wrapped in silver foil were pyrolyzed in an elemental analyzer to afford H_2 and CO in a ceramic reactor packed with glassy carbon. The gases were separated on a GC column, and subjected to IR-MS to obtain the $^2H/^1H$ ratios. The stable isotope ratios are expressed relative to the conventional standard, i.e., VSMOW (Vienna-Standard Mean Ocean Water). The δ values were defined according to the following equation:

$$\delta^{2}H\,(‰) = \left[\frac{R_{sample}}{R_{standard}} - 1\right] \times 1000,$$

where $R = {}^2H/{}^1H$. Each sample was measured five times except for samples No. 22–25. The number of measurement was once for the samples No. 22–25 in Table 4. The repeatabilities routinely obtained were 5‰ or less.

We confirmed that linearity was maintained in the range from 6 V to 10 V for hydrogen and carbon, and 1 V to 5 V for nitrogen by changing the sample amount. A correction factor (H_3^+-factor) was determined by measuring the apparent D/H ratios for H_2 gas pulses of different intensity.

2.3. Substitution of exchangeable hydrogen

Ephedrine/HCl has three exchangeable hydrogen atoms, i.e., in the hydroxyl group (OH), amino group (NH) and HCl, while methamphetamine/HCl has two in NH and HCl. These hydrogen atoms in ephedrine/HCl may be exchanged during the synthesis of methamphetamine from ephedrine, and those of methamphetamine/HCl may be exchanged with ambient water vapor. These labile hydrogen atoms may therefore influence the δ^2H values, so that δ^2H values of ephedrine/HCl and methamphetamine/HCl must be interpreted with caution [15,16]. We searched for appropriate conditions for the exchange to minimize the effect of exchangeable hydrogen atoms. The δ^2H values for standard ephedrine/HCl and standard methamphetamine/HCl treated with water (δ^2H: −233‰) were −82 and −66‰, respectively. The δ^2H values for ephedrine/HCl and methamphetamine/HCl freeze-dried just after dissolution or 24 h after dissolution in Milli Q water were −35 and

Table 1
Ephedrine and pseudoephedrine samples used for measurements of δ^2H, $\delta^{13}C$ and $\delta^{15}N$.

Sample	Origin	Manufacturing method
1 *l*-Ephedrine/HCl	Extracted from ephdra plant	Biosynthetic (I)
2 *l*-Ephedrine/HCl	Extracted from ephdra plant	Biosynthetic (I)
3 *l*-Ephedrine/HCl	Extracted from ephdra plant	Biosynthetic (I)
4 *l*-Ephedrine/HCl	Imported from China	Biosynthetic (I)
5 *l*-Ephedrine/HCl	Extracted from ephdra plant	Biosynthetic (I)
6 *l*-Ephedrine/HCl	Imported from China	Biosynthetic (I)
7 *l*-Ephedrine/HCl	Extracted from ephdra plant	Biosynthetic (I)
8 *d*-Pseudoephedrine/HCl	Extracted from ephdra plant	Biosynthetic (I)
9 *d*-Pseudoephedrine/HCl	Imported from China	Biosynthetic (I)
10 *d*-Pseudoephedrine/HCl	Imported from China	Biosynthetic (I)
11 *l*-Ephedrine/HCl	Purchased from Fujiyakuhin (Japan)	Synthetic (II)
12 *l*-Ephedrine/HCl	Purchased from Marulshi Pharmaceutical (Japan)	Synthetic (II)
13 *l*-Ephedrine/HCl	Purchased from Dainippon Pharmaceutical (Japan)	Synthetic (II)
14 *d*-Pseudoephedrine/HCl	Imported from Taiwan	Synthetic (II)
15 *d*-Pseudoephedrine/$(H_2SO_4)_{1/2}$	Imported from China	Synthetic (II)
16 *l*-Ephedrine/HCl	Imported from India	Semisynthetic (III)
17 *l*-Ephedrine/HCl	Imported from India	Semisynthetic (III)
18 *l*-Ephedrine/HCl	Imported from India	Semisynthetic (III)
19 *l*-Ephedrine/HCl	Imported from India	Semisynthetic (III)
20 *d*-Pseudoephedrine/HCl	Imported from India	Semisynthetic (III)
21 *d*-Pseudoephedrine/HCl	Imported from India	Semisynthetic (III)
22 *d*-Pseudoephedrine/HCl	Imported from India	Semisynthetic (III)
23 *l*-Ephedrine/HCl	Imported from Germany	Semisynthetic (IV)
24 *l*-Ephedrine/HCl	Imported from Germany	Semisynthetic (IV)
25 *d*-Pseudoephedrine/HCl	Imported from Germany	Semisynthetic (IV)
26 *d*-Pseudoephedrine/HCl	Imported from Germany	Semisynthetic (IV)
27 *d*-Pseudoephedrine/HCl	Imported from Germany	Semisynthetic (IV)

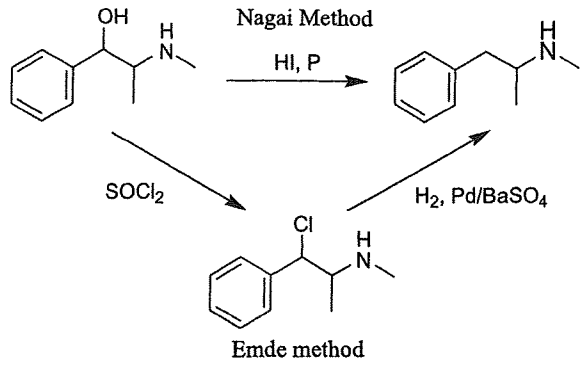

Fig. 1. Synthetic pathways to methamphetamine from ephedrine used in this study.

−37‰, and −38 and −41‰ respectively. These results mean that δ^2H values do not depend on the time taken for preparation of sample solutions. Further, we investigated the relationship of the δ^2H values and the concentration of the sample solution. When the amount of the water was over 5 ml per 5 mg of sample, the δ^2H values became constant. Therefore, we selected 5 mg sample weight in 5 ml of Milli Q water (δ^2H: −62%), with immediate freeze-drying.

3. Results

3.1. δ^2H values of legal ephedrines

We investigated the relationship between the origin of legal ephedrines (shown in Table 1) and the δ^2H values obtained by IR-MS. The δ^2H values for 27 samples are shown in Fig. 2. The δ^2H values for biosynthetic ephedrines were −193 to −151‰, those for synthetic ones were −73 to −30‰, those for semisynthetic ones from molasses were −74 to 243‰, and those for semisynthetic ones from pyruvic acid were 75 to 148‰.

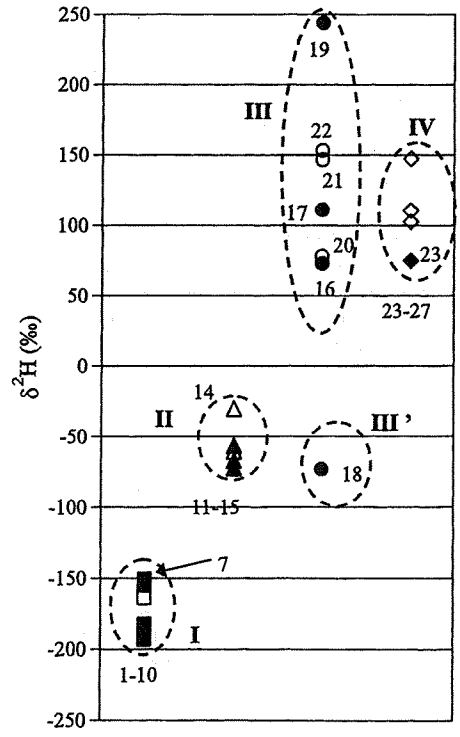

Fig. 2. δ^2H values for *l*-ephedrine and *d*-pseudoephedrine samples: biosynthetic (■), synthetic (▲), semisynthetic from molasses (●) and semisynthetic from pyruvic acid (◆). Open symbols indicate *d*-pseudoephedrine samples. The biosynthetic group is indicated as 'I', the synthetic group as 'II', the semisynthetic group from molasses as 'III', and the semisynthetic group from pyruvic acid as 'IV'.

3.2. $\delta^{13}C$ and $\delta^{15}N$ values of ephedrines

We investigated the origin of 27 legal samples (shown in Table 1) on basis of $\delta^{13}C$ and $\delta^{15}N$ values obtained by IR-MS. The results are shown in Fig. 3. The $\delta^{13}C$ and $\delta^{15}N$ values for biosynthetic ephedrines were −31.1 to −26.0‰ and −2.2 to 10.6‰ respectively, those for synthetic ephedrines were −29.2 to −28.0‰ and −11.0 to −6.4‰ respectively, those values for semisynthetic ephedrines from molasses were −23.7 to −22.0‰ and 2.4 to 7.3‰ respectively, and those for semisynthetic ephedrines from pyruvic acid were −27.5 to −25.3‰ and −4.1 to −2.8‰ respectively.

3.3. Relationships of δ^2H values of precursor ephedrines and synthesized methamphetamine

Table 2 summarizes the δ^2H values for precursor ephedrines and for methamphetamine synthesized from them. Exchangeable hydrogen atoms were substituted as described in Section 2.3. The decrease of δ^2H values in going from ephedrine/pseudoephedrine to the corresponding methamphetamine was in the range from 31 to 50%. The decrease of the δ^2H values means that δ^2H for the benzylic hydrogen of methamphetamine is much lower than the value for the hydrogen of the benzylic hydroxyl group of ephedrine [9,14].

3.4. Effect of exchangeable hydrogen atoms of ephedrines/HCl and methamphetamine/HCl on δ^2H values

The δ^2H values of samples untreated and treated with Milli Q water (as described in Section 2.3) are shown in Table 3. The variations were from +4 to +29‰. The δ^2H values for ephedrine and methamphetamine may be affected by the drying process, the kind of solvent, ambient humidity and so on. In this study, exchangeable hydrogen atoms were substituted in order to eliminate the influence of these atoms on the measured δ^2H values. However, the change in the results due to substitution of exchangeable hydrogens would not have a great influence on the inference as to the origin of the samples.

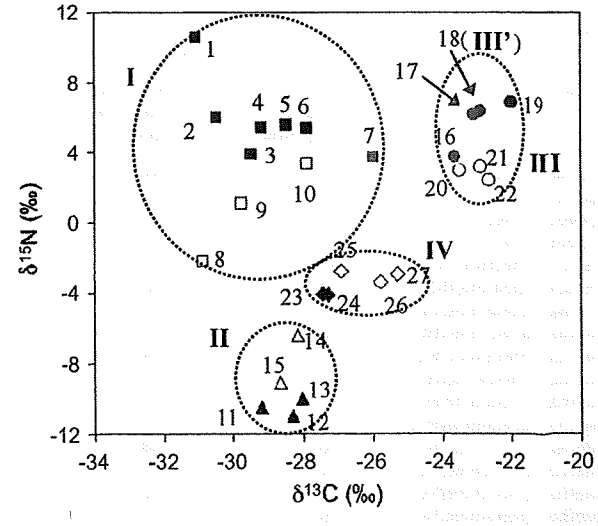

Fig. 3. $\delta^{13}C$ and $\delta^{15}N$ values for *l*-ephedrine and *d*-pseudoephedrine samples: biosynthetic (■), synthetic (▲), semisynthetic from molasses (●), and semisynthetic from pyruvic acid (◆). Open symbols indicate *d*-pseudoephedrine samples. I–IV are the same as in Fig. 2.

Table 2
The δ^2H values of ephedrines used as precursors and the resulting methamphetamine (‰).

Compound	Synthetic pathway	δ^2H	Difference
d-Methamphetamine/HCl (S-1)	Nagai	27	−50
d-Pseudoephedrine/HCl (semisynthetic from molasses)		77	
d-Methamphetamine/HCl (S-2)	Nagai	107	−41
d-Pseudoephedrine/(semisynthetic from pyruvic acid)		148	
d-Methamphetamine/HCl (S-3)	Nagai	33	−38
l-Ephedrine/HCl (semisynthetic from molasses)		71	
d-Methamphetamine/HCl (S-4)	Nagai	38	−37
l-Ephedrine/HCl (semisynthetic from pyruvic acid)		75	
d-Methamphetamine/HCl (S-5)	Nagai	−175	−36
l-Ephedrine/HCl (biosynthesis)[a]		−139	
d-Methamphetamine/HCl (S-6)	Emde	−180	−41
l-Ephedrine/HCl (biosynthesis)[a]		−139	
d-Methamphetamine/HCl (S-7)	Nagai	−215	−31
l-Ephedrine/HCl (biosynthesis)		−184	

[a] *l*-Ephedrine/HCl is same.

Table 4
Stable isotope ratios of seized methamphetamine samples (‰).

Sample	δ^2H	$\delta^{13}C$	$\delta^{15}N$
1	−237	−28.7	6.1
2	−230	−28.7	6.1
3	−228	−29.4	7.3
4	−227	−28.7	6.4
5	−224	−28.5	6.2
6	−212	−29.9	6.6
7	−208	−27.6	4.2
8	−206	−27.2	4.8
9	−204	−27.6	4.4
10	−202	−26.9	2.9
11	−200	−27.1	3.0
12	−196	−29.4	5.4
13	−195	−29.5	5.8
14	−192	−26.9	1.5
15	−180	−27.0	3.3
16	−122	−31.9	0.3
17	−107	−30.3	0.6
18	−64	−32.8	2.0
19	−18	−32.5	3.1
20	−1	−23.1	5.1
21	47	−23.3	9.4
22	19	−26.3	−2.6
23	41	−26.2	−3.2
24	45	−26.1	−3.0
25	46	−26.2	−2.2

3.5. Stable isotope ratio of seized samples

We applied the IR-MS technique to identify the origin of two ephedrine/HCl samples seized in Myanmar. The δ^2H, $\delta^{13}C$ and $\delta^{15}N$ values were −54, −23.1 and 7.1, and −53, −23.7 and 7.3 respectively. Table 4 summarizes the δ^2H, $\delta^{13}C$ and $\delta^{15}N$ values of methamphetamine samples seized in Japan.

4. Discussion

The δ^2H values of biosynthetic ephedrines (I) showed a remarkable difference from those of synthetic (II) and semisynthetic ephedrines (III and IV) in Fig. 2. In a plot of $\delta^{13}C$ versus $\delta^{15}N$, semisynthetic ephedrines from pyruvic acid (IV, No. 23–27) were distinct from cluster III of semisynthetic ephedrines from molasses, as shown in Fig. 3. But, the semisynthetic ephedrines (IV, No. 23–27) were located close to biosynthetic ephedrines (I) and synthetic ephedrines (II) in the plot of $\delta^{13}C$ versus $\delta^{15}N$. Thus, classification is not clear-cut based on $\delta^{13}C$ versus $\delta^{15}N$. Ternary isotope plots of δ^2H, $\delta^{13}C$ and $\delta^{15}N$ in three-dimensions provided a graphical illustration of the discrimination of commercial ephedrines (Fig. 4). Four ephedrines (I–IV) used in this study were respectively dispersed into well-defined clusters in combination of δ^2H, $\delta^{13}C$ and $\delta^{15}N$. No. 8 sample is clearly confirmed to be biosynthetic ephedrine in Fig. 4. Similarly, No. 23 and 24 samples are confirmed to be semisynthetic ephedrine from pyruvic acid. The semisynthetic ephedrines from molasses were grouped into one in Fig. 4, but in detail they could be profiled into two groups (III and III′) by using the value of δ^2H (Fig. 2). This means that δ^2H value is very useful for in-depth drug profiling. It is presumed that the lower deuterium content of No.18 sample (δ^2H: −74‰) may be due to the use of benzaldehyde from natural source or hydrolysis of benzal chloride at the manufacturing process [14,17]. We applied the IR-MS technique to identify the origin of two ephedrine/HCl samples seized in Myanmar. Since they were located close to No. 18 ephedrine in Fig. 4, it is presumed that the origin of the seized

Table 3
The δ^2H values of samples untreated and treated with Milli Q water (‰).

Sample	δ^2H of samples untreated with Milli Q water	δ^2H of samples treated with Milli Q water	Change in δ^2H
l-Ephedrine/HCl	−203	−184	19
l-Ephedrine/HCl	−151	−139	12
l-Ephedrine/HCl	65	71	14
l-Ephedrine/HCl	63	75	12
d-Pseudoephedrine/HCl	65	77	12
d-Pseudoephedrine/HCl	120	148	28
d-Methamphetamine/HCl	−237	−220	17
d-Methamphetamine/HCl	−228	−224	4
d-Methamphetamine/HCl	−212	−198	14
d-Methamphetamine/HCl	−204	−197	7
d-Methamphetamine/HCl	−200	−178	22
d-Methamphetamine/HCl	−195	−184	11
d-Methamphetamine/HCl	−180	−168	12
d-Methamphetamine/HCl	−124	−99	25
d-Methamphetamine/HCl	−107	−92	15
d-Methamphetamine/HCl	−89	−73	16
d-Methamphetamine/HCl	−64	−45	19
d-Methamphetamine/HCl	−18	−6	12
d-Methamphetamine/HCl	−1	28	29
d-Methamphetamine/HCl	47	62	15

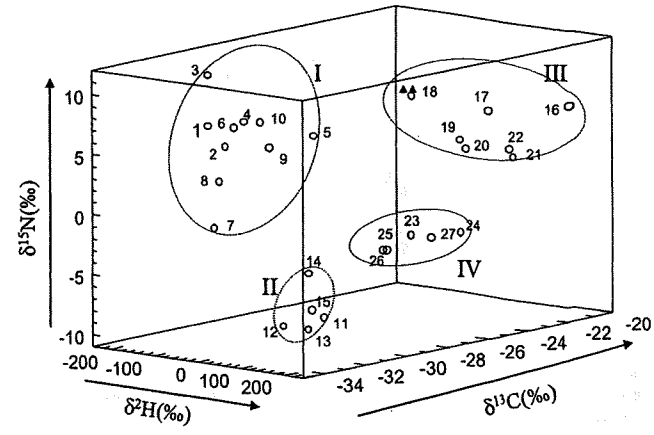

Fig. 4. Ternary isotope plots of δ^2H, $\delta^{13}C$ and $\delta^{15}N$ in three-dimensions of ephedrines: numbers from 1 to 27 are the same as in Fig. 2. Seized samples are plotted as a triangle (▲). I–IV are the same as in Fig. 2.

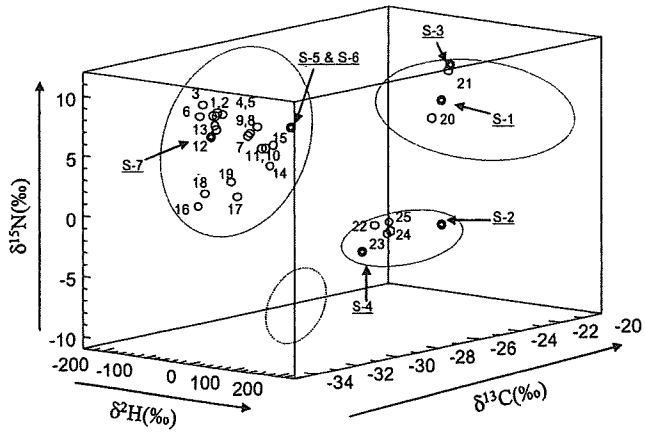

Fig. 5. Ternary isotope plots of δ^2H, $\delta^{13}C$ and $\delta^{15}N$ in three-dimensions of methamphetamine: numbers from 1 to 25 are assigned to the seized samples in Table 4. Marks from S-1 to S-7 are 7 methamphetamines synthesized from known ephedrines in Table 2.

ephedrine may be similar to semisynthetic ephedrine III'. With same scale and three-dimensions as shown in Fig. 4, Fig. 5 shows the ternary isotope plots of δ^2H, $\delta^{13}C$ and $\delta^{15}N$ for synthesized (seven samples in Table 2) and seized methamphetamines (25 samples in Table 4). Since each synthesized methamphetamine was located to the cluster of each origin of ephedrines used as precursors, it can be presumed that the decrease of δ^2H values of precursor ephedrines were not so greatly changed in the synthesized methamphetamine to disturb the discrimination (Fig. 5). It is presumed that the IR-MS analysis of seized methamphetamine will give an appropriate screening for the manufacturing process of ephedrines used as precursor. For example, it can be clearly inferred that samples No. 1–19 in Table 4 were synthesized from biosynthetic ephedrine on the basis of the location in Fig. 5. Similarly, it can be presumed that methamphetamine samples No. 20 and 21 were synthesized from semisynthetic ephedrine (molasses group) and No. 22–25 from semisynthetic ephedrines (pyruvic acid group). Therefore, the δ^2H value is useful in determining the manufacturing process of ephedrine used to prepare methamphetamine, in combination with the values of $\delta^{13}C$ and $\delta^{15}N$.

5. Conclusion

Measurement of δ^2H, $\delta^{13}C$ and $\delta^{15}N$ values by IR-MS appears to be effective for discrimination of the manufacturing process of ephedrines. The inclusion of δ^2H analysis enables us to discriminate ephedrines having similar $\delta^{13}C$ and $\delta^{15}N$ values. In general, hydrogen isotope patterns are obtainable with ^2H NMR or isotope ratio mass spectrometry (IR-MS), and are useful to trace a substance's origin [9–14]. The hydrogen isotope patterns in this study were consistent with the site-specific deuterium contents observed with ^2H-NMR in our previous work [9]. IR-MS requires only about 10 min per measurement, and the IR-MS technique is expected to be very useful for profiling of methamphetamine and monitoring the source of ephedrines used for clandestine manufacture of methamphetamine. This study was carried out on a limited number of ephedrines samples, reflecting the various routes of ephedrine manufacture, and our results confirm the feasibility of using hydrogen stable isotope ratio in combination with the values of $\delta^{13}C$ and $\delta^{15}N$ for profiling ephedrine and methamphetamine. A larger-scale study seems warranted. This approach should be a useful tool in worldwide precursor control of methamphetamine.

Acknowledgments

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