Investigation of the origin of ephedrine and methamphetamine by stable isotope ratio mass spectrometry: a Japanese experience*

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ABSTRACT

Illicit drug abuse is a serious global problem that can only be solved through international cooperation. In Asian countries, the abuse of methamphetamine is one of the most pressing problems. To assist in the control of methamphetamine, the authors investigated in detail the character of ephedrine, which is a key precursor for the illicit manufacture of methamphetamine.

Commercial ephedrine is produced by one of three methods: (a) *extraction from* Ephedra *plants,* (b) *full chemical synthesis or* (c) *via a semi-synthetic process involving the fermentation of sugar, followed by amination. Although chemically there is no difference between ephedrine samples from different origins (natural, synthetic or semi-synthetic), scientific and analytical tools such as drug-characterization and impurity-profiling programmes may provide valuable information for law enforcement and regulatory activities as part of precursor control strategies.*

During the research under discussion in the present article, in addition to classical impurity profiling of manufacturing by-products, the use of stable isotope ratio mass spectrometry was investigated for determining the origin of the ephedrine that had been used as a precursor in seized methamphetamine samples. The results of carbon and nitrogen stable isotope ratio ($\delta^{13}C$ and $\delta^{15}N$) analysis of samples of crystalline methamphetamine seized in Japan suggested that the drug had been synthesized from either natural or semi-synthetic ephedrine and not from synthetic ephedrine.

Stable isotope ratio analysis is expected to be a useful tool for tracing the origins of seized methamphetamine. It has attracted much interest from precursor control authorities in Japan and the East Asian region and may prove useful in the international control of precursors.

Keywords: drug profiling; IRMS; methamphetamine; ephedrine; precursor; origin.

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Introduction

Illicit drug abuse is a serious global problem that can only be solved through international cooperation. The abuse of methamphetamine is one of the most pressing drug problems in Asian countries. Methamphetamine is illicitly produced across the region, as demonstrated by the dismantling of clandestine laboratories in China, Indonesia, Malaysia, Myanmar, the Philippines, Taiwan Province of China and Viet Nam. At many such laboratories, precursors and chemicals for methamphetamine production have been seized together with crystalline methamphetamine.

The prevention of production is one of the most effective drug control measures. In the case of synthetic drugs, precursor control is an important component of the strategy for preventing production. Many government agencies have cooperated in international activities to prevent the diversion of precursors and chemical substances, such as Operation Topaz to counter the illicit production of heroin, Operation Purple against cocaine and Project Prism against amphetamine-type stimulants (ATS). International efforts to monitor the distribution of precursor chemicals and to promote the rapid exchange of information about suspicious imports and exports have met with some success. For example, chemical information from drug impurity profiling programmes is increasingly recognized as a valuable supplement to precursor control strategies. Information about precursors and synthetic routes of illicit manufacture may help drug law enforcement authorities trace the source of precursors or obtain other information of strategic relevance.

In view of the extent of the problem of methamphetamine abuse in Japan and the East and South-East Asian regions, Japan has taken a significant interest in this field. At two expert meetings held in Japan, recognition was accorded to the role of drug experts and scientists in facilitating the sharing of chemical information on illicit drugs and the development of analytical methods under the coordination of the United Nations Office on Drugs and Crime (UNODC). The first of the two meetings was a consultative one on profiling and the characterization of methamphetamine and other ATS, organized by UNODC and held in Tokyo in 1998, and the second was a Group of Eight (G8) ad hoc meeting of drug experts, held in Miyazaki in 2000. In addition, as part of the overall drug control approach with a focus on ATS in the Japanese five-year plan, Japan also hosted two international forums on the control of precursors for ATS; these were held in 2004 and 2005.

In terms of chemical analytical research, Japan has been involved for some years in developing methods for the impurity profiling of methamphetamine [1-3]. More recently, the research group responsible for the research under discussion in the present article has also investigated carbon and nitrogen stable isotope ratio analysis as a promising new tool for the characterization of methamphetamine [4].

This technique already has an established place in the fields of biochemistry and food chemistry, where it is used to identify the geographical

origin of natural products, such as tea, wine and honey. It is based on the fact that most elements exist in several different isotopic forms (that is, forms of the same element that differ slightly in their atomic masses) and that the abundances of the different isotopes vary according to environmental conditions, thus allowing a differentiation according to origin.

Since ephedrine, the main precursor for the synthesis of methamphetamine, may be of natural, semi-synthetic or synthetic origin, the research team investigated whether the stable isotope ratio values for carbon and nitrogen enabled the discrimination of ephedrine according to its origin. It was further investigated whether the carbon and nitrogen stable isotope ratio values of ephedrine used as a precursor were correlated with the corresponding values in the end product, methamphetamine.

The present article describes the approaches to sample comparison with the overall aim of identifying the sources and synthesis routes of illicitly manufactured methamphetamine and its precursors, in particular ephedrine. Preliminary research is presented on the potential of a promising new technique, carbon and nitrogen stable isotope ratio analysis by isotope ratio mass spectrometry (IRMS) [4], together with an application example for some methamphetamine samples. The usefulness and limitations of chemical information in drug precursor control are discussed.

Comparative analyses

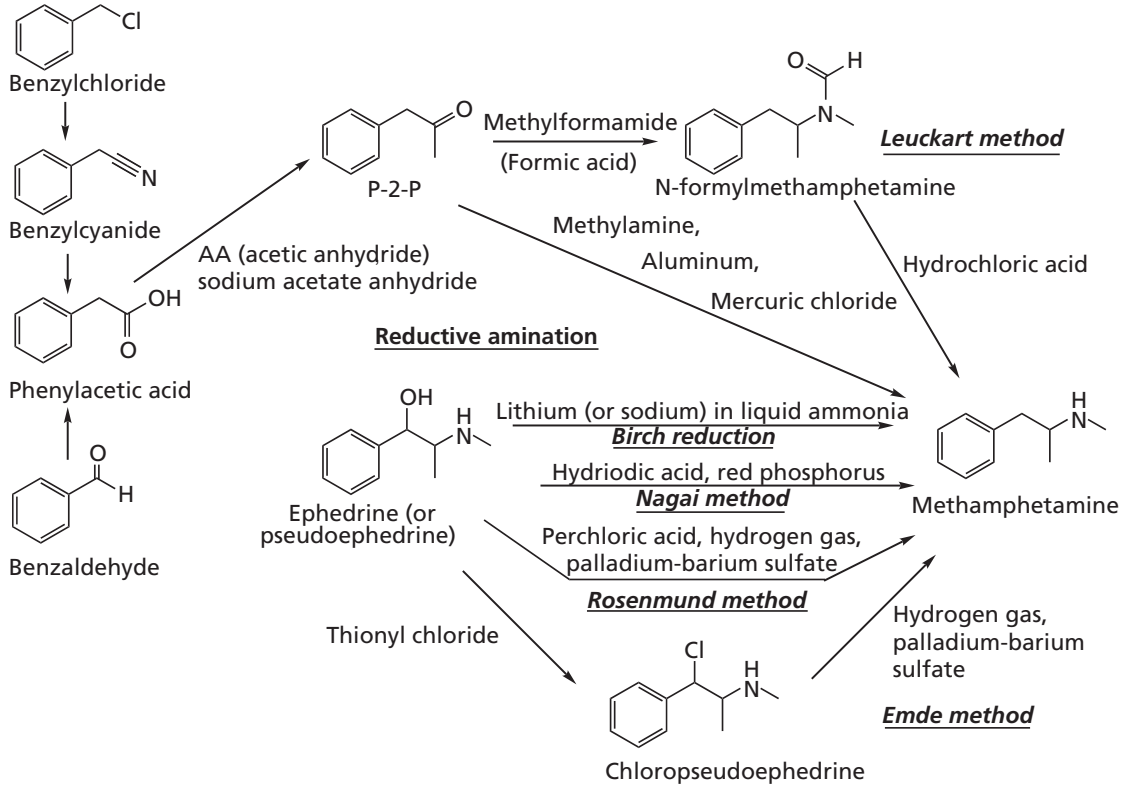
Determination of the synthetic route of methamphetamine by impurity profiling

Methamphetamine is synthesized in clandestine laboratories by a variety of routes, as shown in figure I [5]. The two main precursors used for clandestine methamphetamine synthesis are ephedrine (or pseudoephedrine), and 1-phenyl-2-propanone (P-2-P). Clandestine methamphetamine often contains impurities arising from incomplete reaction.

The traditional means of comparative sample analysis of illicitly manufactured drugs is a technique known as "drug characterization/impurity profiling". It is based on the analysis of impurities and by-products from the manufacturing process, that is, organic compounds that are present in the illicit drug end product due to clandestine manufacturing conditions.

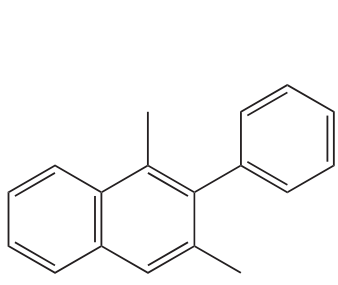
Many methods have been reported for the isolation and identification of the characteristic impurities of the various synthetic pathways of methamphetamine [1, 6-9]. In a study funded by a health sciences research grant from the Ministry of Health, Labour and Welfare of Japan, the impurity profiling of methamphetamine was investigated, focusing on the synthetic route and the precursor [3, 10-12]. As part of the research activities, methamphetamine was synthesized in the laboratory by the four main synthetic methods, that is, the Nagai, Emde and Leuckart methods and reductive amination (see figure I), and

Figure I. Interrelationship of methamphetamine and main precursor substances

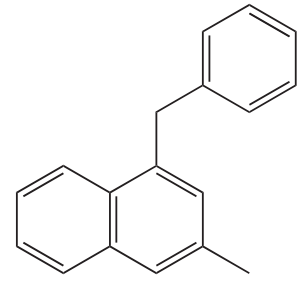


the impurities specific to each method were identified from among the many impurities generated. The following compounds were identified as key route-specific impurities:

1. Naphthalenes (1,3-dimethyl-2-phenylnaphthalene and/or 1-benzyl-3-methylnaphthalene)

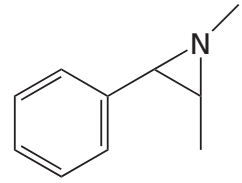


1,3-dimethyl-2-phenylnaphthalene



1-benzyl-3-methylnaphthalene

2. Aziridines (*cis*- and/or *trans*-1,2-dimethyl-3-phenylaziridine)

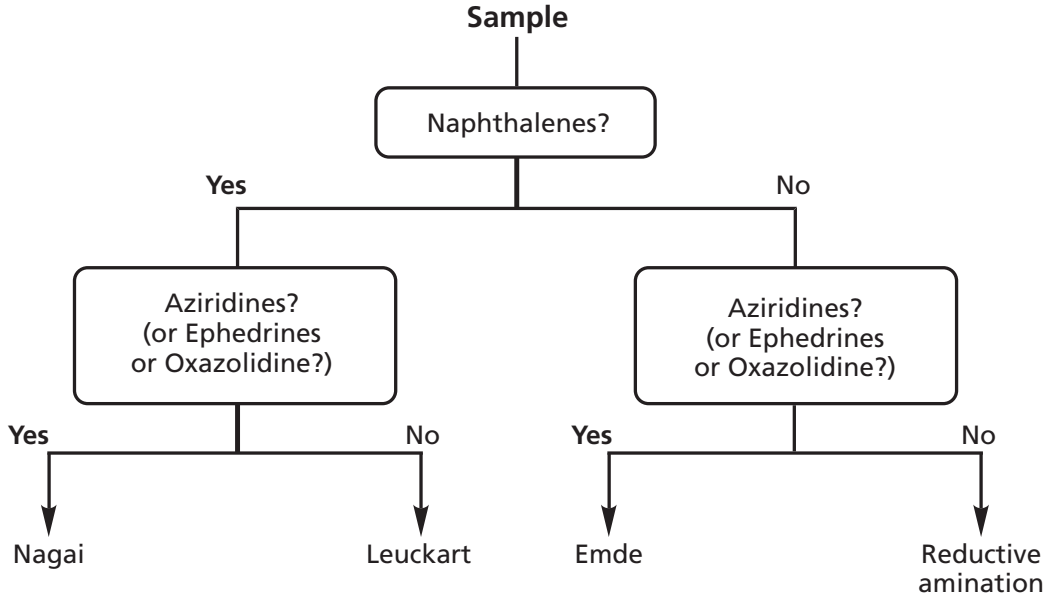


cis/*trans*-1,2-dimethyl-3-phenylaziridine

Specifically, it was found that the naphthalenes were generated only in methamphetamine synthesized via the Nagai and Leuckart methods and were not formed in the Emde method or during reductive amination. Aziridines were detected only in the cases of the Nagai and Emde methods.

The impurities could be detected by gas chromatography-mass spectrometry (GC-MS). In some cases, the aziridines were difficult to detect in methamphetamine prepared by the Nagai or Emde methods. In those cases, confirmation by GC-MS or high pressure liquid chromatography of the presence of trace amounts of ephedrine or a compound related to ephedrine, that is, erythro-3,4-dimethyl-5-phenyloxazolidine (oxazolidine), may be required [3, 10, 13]. The results are summarized in the flow chart shown in figure II, which presents a decision tree based on the presence in crystalline methamphetamine samples of a limited set of route-specific impurities.

Figure II. Flow chart for identifying the synthetic route used in the preparation of methamphetamine samples



As a result of this work it has become possible to infer the synthetic route by looking for route-specific impurities [11, 12]. Using this approach, it was possible to confirm that most methamphetamine samples seized in Japan were manufactured from ephedrine. Given the relevance of this precursor, it deserves further investigation, as detailed below.

Determination of the origin of ephedrine from the stable isotope ratios of carbon and nitrogen

The basis for stable isotope ratio analysis lies in the fact that most elements exist in several different isotopic forms (that is, forms of the same element that differ slightly in their atomic masses), and that the abundances of the different

isotopes vary according to environmental conditions. For example, the natural abundance of nitrogen-14 (^{14}N) is 99.635 per cent and that of nitrogen-15 (^{15}N) is 0.365 per cent. Isotopes have slightly different chemical and physical properties because of their mass differences. Heavy isotopes undergo the same chemical reactions as light isotopes, but react more slowly. Such slight differences in reaction rate mean that products have isotope ratios that differ from those of the source materials.

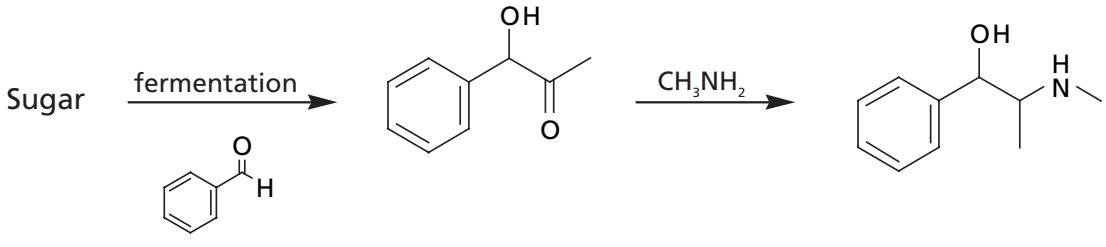
Stable isotope ratios are determined as per mille (‰) differences, that is, in units of parts per thousand, relative to international standard materials and are expressed, for example, for carbon and nitrogen as $\delta^{13}C$ and $\delta^{15}N$ respectively. In principle, precise analysis of stable isotope ratios enables investigation of the circulation of materials on a global scale and the estimation of the contribution of physical or biological factors.

Commercial ephedrine, one of the key precursors of methamphetamine, is produced by one of three processes, as shown in figure III. Natural ephedrine is prepared by extraction from *Ephedra* plants. This process is typically employed for ephedrine manufactured in China. Semi-synthetic ephedrine is prepared by fermentation of sugar followed by amination, a process known to be used in India. Fully chemically synthesized ephedrine is produced elsewhere.

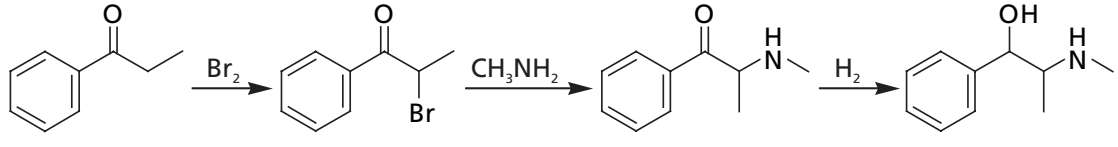
Figure III. Production schemes of ephedrine

(1) Extraction from *Ephedra* plants

(2) Fermentation of sugar followed by amination



(3) Chemical synthesis: bromination of propiophenone followed by amination



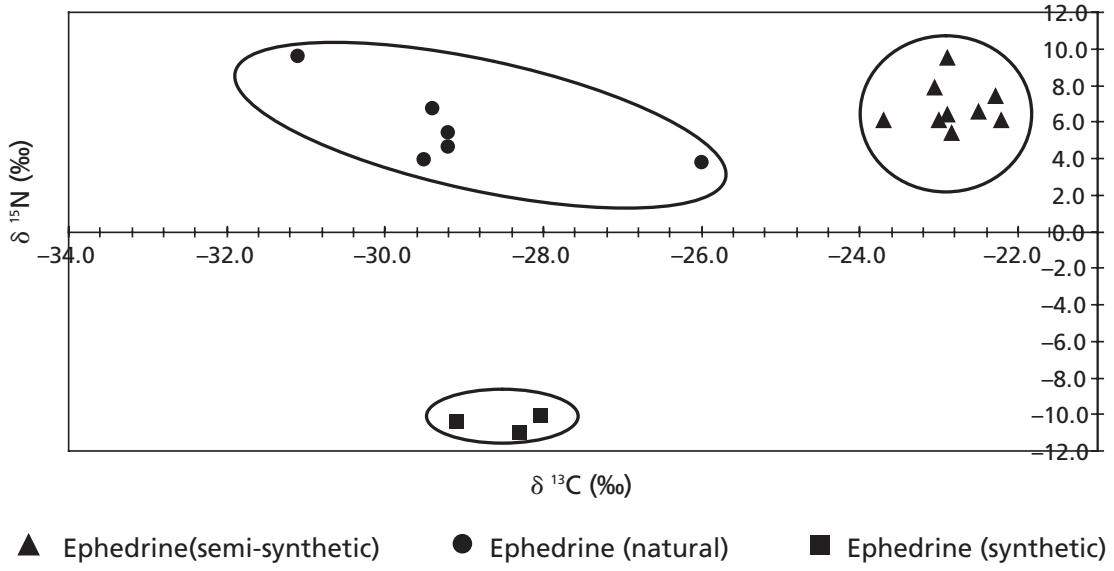
As can be seen in figure III, in the case of natural ephedrine (1), the entire molecule is isolated from plant material and is therefore of natural origin. In cases (2) and (3), different parts of the molecule may be from different sources, with the pre-precursors possibly also being from different natural, semi-synthetic or synthetic origins. In cases (2) and (3), the nitrogen source is methylamine (CH_3NH_2), which is added in step two of the manufacturing process.

In the research, it was investigated whether the stable isotope ratio values for carbon and nitrogen allowed the discrimination of ephedrine according to its origin (natural, semi-synthetic or synthetic). In a second step, it was further investigated whether the carbon and nitrogen stable isotope ratio values of ephedrine used as a precursor were correlated with the corresponding values in the end product, methamphetamine.

When the use of ephedrine as a precursor has been confirmed by classical drug impurity profiling as described above, the stable isotope ratio analysis of carbon and nitrogen may give further useful information to discriminate the origin of ephedrine.

Figure IV shows the carbon ($\delta^{13}C$) and nitrogen ($\delta^{15}N$) stable isotope ratios of ephedrine samples of different origins, determined using IRMS.

Figure IV. Ephedrine: carbon and nitrogen isotope ratios



Note: The experimental conditions were as follows [4]:

Instrument: stable isotope ratio mass spectrometer Delta^{Plus} (ThermoFinnigan, United States of America), equipped with an elemental analyser flash EA1112 (ThermoFinnigan).

Sample size: 250 μg.

Stable isotope ratios (average of five analyses) are expressed relative to the conventional standards: Peedee Belemite for carbon and atmospheric N_2 for nitrogen.

Precision: 0.1‰ or less for ^{13}C, and 0.2‰ or less for ^{15}N.

Focusing on the $\delta^{15}N$ values of the samples examined (y-axis), figure IV shows that there are indeed remarkable differences between synthetic ephedrine (■) on the one hand, and natural (●) and semi-synthetic (▲) ephedrine on the other. $\delta^{15}N$ values are smaller (more negative) in the samples of fully chemically synthesized ephedrine than in those of natural or semi-synthetic ephedrine.

With regard to $\delta^{13}C$ values (x-axis), figure IV shows that the values of the samples of natural and synthetic ephedrine examined were lower (more negative) than those of semi-synthetic ephedrine. Figure IV also shows that the $\delta^{13}C$ values of the natural ephedrine samples examined were widely dispersed, from −31.1 to −26.0 units of parts per thousand.

Sources of nitrogen

The nitrogen in an ephedrine molecule may be of natural origin in the case of ephedrine of natural origin or it may be introduced as part of a synthesis step in synthetic and semi-synthetic ephedrine (see figure III). The source of nitrogen in the cases of synthetic and semi-synthetic ephedrine is methylamine, which may itself be of natural origin or prepared by the chemical reaction of ammonia and methanol, then purified by distillation. With regard to the latter, synthetic methylamine, it was shown in earlier work [4] that the nitrogen-15 isotope ratio of methylamine changed to more negative values with successive distillations. It is assumed that this is the result of stable nitrogen isotope fractionation in the distillation step.

The low $\delta^{15}N$ values of the samples of fully chemically synthesized ephedrine in figure IV suggest the use of synthetic, purified methylamine for the manufacture of those samples. If synthetic, purified methylamine had also been used for manufacture of the semi-synthetic ephedrine samples in figure IV, then the $\delta^{15}N$ value would be expected to be similar to that of chemically synthesized ephedrine. However, figure IV shows that the $\delta^{15}N$ value of semi-synthetic ephedrine is similar to that of natural ephedrine. This suggests that methylamine extracted from biological sources (plants) may have been used for the semi-synthetic ephedrine samples examined.

Sources of carbon

In plants, there are two main routes of photosynthesis, C3 and C4. C3-photosynthesis is characterized by the formation of a three carbon-atom molecule during the first steps of carbon dioxide assimilation. It occurs in plants of temperate origin, such as sugar beets, tobacco, clover and soybeans, so-called C3-plants. All major plant families, or about 90 per cent of all plant species on Earth, are C3-plants. The C4-photosynthesis initially produces four carbon-atom molecules and occurs in plants of tropical origin, such as sugar cane, cotton and corn. It is reported that C4-plants contain more carbon-13 than C3-plants [14-15].

Sugar from sugar cane (a C4-plant) is the typical starting material for semi-synthetic ephedrine. *Ephedra*, by contrast, the raw material for natural ephedrine, is a C3-plant. It was anticipated that the characteristics of the starting material would be reflected in the $\delta^{13}C$ values of the ephedrine produced.

As shown in figure IV and noted above, the $\delta^{13}C$ values of natural ephedrine are lower (more negative) than those of semi-synthetic ephedrine and are dispersed widely from −31.1 to −26.0 units of parts per thousand. It was presumed that the wide variations of $\delta^{13}C$ values of natural ephedrine reflected differences in humidity and other conditions in the growing areas. Further work using authenticated ephedrine samples from *Ephedra* plants of known geographical origin will be needed to test this hypothesis.

d-Pseudoephedrine, another key precursor of methamphetamine, is usually manufactured from *l*-ephedrine by acid isomerization. Figure V shows the results of carbon and nitrogen stable isotope ratio analysis of samples of pseudoephedrine obtained from different manufacturers (A-F), together with the corresponding results of ephedrine samples given in figure IV.

It can be seen that the $\delta^{15}N$ values of *d*-pseudoephedrine from Manufacturer A (Δ) are lower than that of semi-synthetic ephedrine (▲), but significantly higher than those of synthetic ephedrine (■), while $\delta^{13}C$ values of *d*-pseudoephedrine are comparable with those of semi-synthetic ephedrine. Background information from Manufacturer A indeed confirms that the samples were manufactured from semi-synthetic ephedrine and that both the ephedrine and pseudoephedrine samples had the same country of origin. It is presumed that the observed lower $\delta^{15}N$ value of *d*-pseudoephedrine is a result of nitrogen isotope fractionation during the manufacturing (isomerization) process, similar to the impact of successive distillations on nitrogen-15 values in methylamine.

Figure V. Ephedrine and pseudoephedrine: carbon and nitrogen isotope ratios

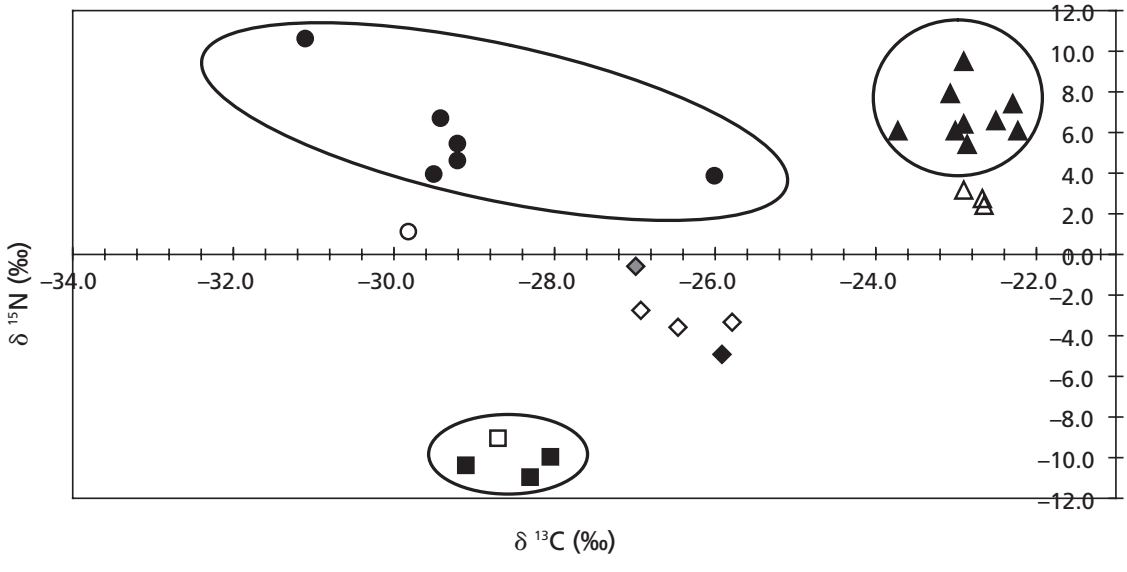


Figure V also shows $\delta^{15}N$ and $\delta^{13}C$ values of *d*-pseudoephedrine samples from five other manufacturers (B, C, D, E and F). For samples of Manufacturer C (◇), not only $\delta^{15}N$, but also $\delta^{13}C$ values were lower than the corresponding values of semi-synthetic ephedrine (▲). Background information from Manufacturer C suggests that the samples were imported from Europe. Assuming that semi-synthetic ephedrine in Europe would be manufactured from sugar beets instead of sugar cane as starting material, it is presumed that the lower $\delta^{13}C$ value is a reflection of the differences between a C3-plant (sugar beet) and a C4-plant (sugar cane). The lower $\delta^{15}N$ value is, again, presumed to be a result of nitrogen fractionation during the isomerization process.

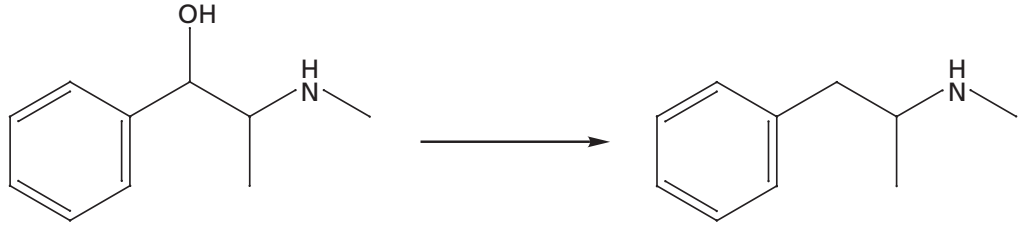
The team was informed that the sample from Manufacturer B (○) was prepared from natural ephedrine and the sample from Manufacturer F (□) was synthesized chemically, thus confirming the IRMS results. Samples from Manufacturers D and E were reagent-grade pseudoephedrine available on the chemicals market. Their close proximity to pseudoephedrine from Manufacturer C suggests that these samples, too, were manufactured from European semi-synthetic ephedrine.

Carbon and nitrogen stable IRMS thus has the potential to discriminate between ephedrine of natural, semi-synthetic and synthetic origin. In order to make full operational use of the results obtained, comprehensive knowledge of the manufacturing processes employed by legitimate manufacturers and the nature and origins of the raw materials used are required. Further, if authentic sample material from many pharmaceutical companies was available, and if it was possible to differentiate ephedrine samples from different manufacturers, this technique may enable the source (manufacturer) of ephedrine and pseudoephedrine to be identified.

Relationship between ephedrine (precursor) and methamphetamine (end product) based on the stable isotope ratios of carbon and nitrogen

The clandestine manufacture of methamphetamine from ephedrine only consists of the elimination of a hydroxyl group from the ephedrine molecule, with all other parts of the molecule remaining unchanged (figure VI). As a result, the synthesized methamphetamine has the same carbon, hydrogen and nitrogen atoms as the precursor ephedrine and it can be expected that the carbon and nitrogen stable isotope ratios of both precursor and end product are closely related.

Figure VI. Schematic presentation of the manufacture of methamphetamine (right) from ephedrine (left)



To investigate whether the carbon and nitrogen stable isotope ratios of ephedrine are carried through to the end product, methamphetamine was synthesized in the laboratory from ephedrine of three different origins by means of the Nagai method. The results, shown in table 1, show that $\delta^{13}C$ and $\delta^{15}N$ values for the precursor were indeed well correlated with those for the end product. This suggests that IRMS may be a useful analytical tool to link precursor and end product.

Table 1. Comparison of $\delta^{13}C$ and $\delta^{15}N$ values of ephedrine precursor and methamphetamine end product

Sample	*$\delta^{13}C$ (‰)*	*$\delta^{15}N$ (‰)*
Natural ephedrine	–29.2	+4.2
Methamphetamine from the above natural ephedrine	–29.5	+3.9
Semi-synthetic ephedrine	–23.1	+6.2
Methamphetamine from the above semi-synthetic ephedrine	–23.1	+5.8
Synthetic ephedrine	–29.2	–10.5
Methamphetamine from the above synthetic ephedrine	–29.2	–11.1

Application example: profiling of seized crystalline methamphetamine by means of key impurity analysis and carbon and nitrogen stable isotope ratio analysis

A total of 15 samples of crystalline methamphetamine seized in Japan, with law enforcement information as to the presumed source countries, were investigated by impurity profiling and stable isotope ratio analysis. Brief information on each sample and the synthetic route identified by impurity profiling, using the flow scheme in figure II, are listed in table 2. Figure VII shows the $\delta^{13}C$ and $\delta^{15}N$ values of the different samples as a two-dimensional plot.

Table 2. List of methamphetamine samples used for impurity profiling and stable isotope mass spectrometry analysis

	Information on methamphetamine	*Estimated synthetic pathway*
1.	Crystals seized in the Sea of Japan near Ishikawa Prefecture in 1999	Emde method
2.	Crystals smuggled into Japan from Hong Kong Special Administrative Region of China via Incheon airport, Republic of Korea, by five Koreans in 2002	Nagai method
3.	Crystals smuggled into Japan from Malaysia	Emde method
4.	Crystalline methamphetamine from Dainippon Pharmaceutical (renamed Dainippon Sumitomo Pharma on 1 October 2005) (Japan)	Emde method

Table 2 *(continued)*

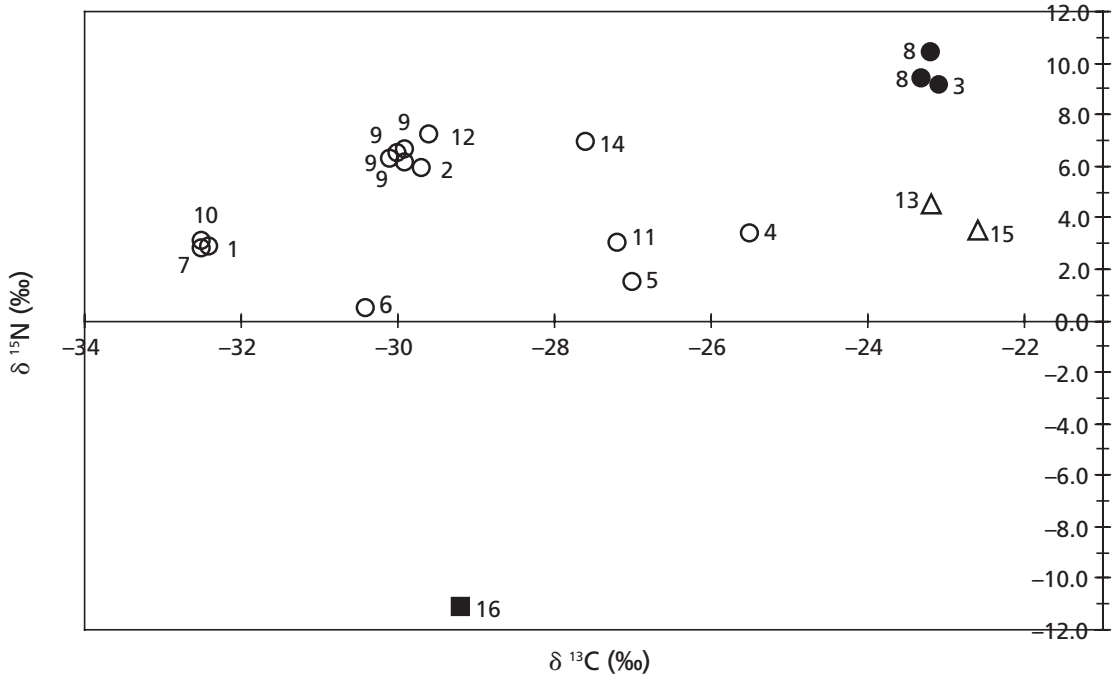
	Information on methamphetamine	*Estimated synthetic pathway*
5.	Crystals seized on a ship registered in China at the port of Sakai, Shimane Prefecture, smuggled into Japan from a port of origin in the Democratic People's Republic of Korea in 1999	Emde method
6.	Crystals seized on a ship registered in the Democratic People's Republic of Korea at the port of Hamada, Tottori Prefecture, in 1999	Emde method
7.	Crystals smuggled from the Philippines	Emde method
8.	Crystals from Canada seized at Narita airport in 2003	Nagai method
9.	Crystals from Canada seized at Narita airport in 2003	Emde method
10.	Crystals seized in the East China Sea near Kagoshima Prefecture in 1999	Emde method
11.	Crystals seized at the port of Yokohama in 2004	Nagai method
12.	Crystals seized at the port of Hosojima, Miyazaki Prefecture, in 1997	Emde method
13.	Crystals seized in Australia	Nagai method
14.	Crystals seized in the Republic of Korea	Emde method
15.	Crystals seized in the United States of America	Nagai method

Using stable carbon and nitrogen isotope ratios as indicators, the results suggest that the precursor of all seized methamphetamine samples investigated was natural or semi-synthetic ephedrine, not synthetic ephedrine. This is consistent with information from drug law enforcement authorities. More specifically, for the samples investigated, the following conclusions about the relationship of precursor and product can be drawn:

- The $\delta^{13}C$ and $\delta^{15}N$ values of samples from Canada (8) and Malaysia (3) agree very closely with those of semi-synthetic ephedrine;
- The values of samples seized in Australia (13) and in the United States (15) agree very closely with those of semi-synthetic pseudoephedrine;
- The values of a few samples seized in Japan (1 and 10) and one sample smuggled from the Philippines (7) agree closely with those of natural ephedrine;
- Considering the observed wide dispersion of $\delta^{13}C$ values of natural ephedrine shown in figure IV, the values of several other methamphetamine samples, such as samples 2 and 9 with law enforcement links to the Republic of Korea and Canada respectively, and possibly also samples 5, 11 and 14, can be assumed to have been manufactured from natural ephedrine.

The findings for sample 8 from Canada are supported by reports suggesting that large amounts of medical ephedrine or pseudoephedrine are imported into Canada from India, where the major product is semi-synthetic ephedrine [16].

Figure VII. Methamphetamine: carbon and nitrogen isotope ratios



Legend:

1 Crystals seized in the Sea of Japan near Ishikawa Prefecture in 1999.

2 Crystals smuggled into Japan from Hong Kong Special Administrative Region of China via Incheon airport, Republic of Korea, by five Koreans in 2002.

3 Crystals smuggled into Japan from Malaysia.

4 Crystalline methamphetamine from Dainippon Pharmaceutical (renamed Dainippon Sumitomo Pharma on 1 October 2005) (Japan).

5 Crystals seized on a ship registered in China at the port of Sakai, Shimane Prefecture, smuggled into Japan from a port of origin in the Democratic People's Republic of Korea in 1999.

6 Crystals seized on a ship registered in the Democratic People's Republic of Korea at the port of Hamada, Tottori Prefecture, in 1999.

7 Crystals smuggled from the Philippines.

8 Crystals from Canada seized at Narita airport in 2003.

9 Crystals from Canada seized at Narita airport in 2003.

10 Crystals seized in the East China Sea near Kagoshima Prefecture in 1999.

11 Crystals seized at the port of Yokohama in 2004.

12 Crystals seized at the port of Hosojima, Miyazaki Prefecture, in 1997.

13 Crystals seized in Australia.

14 Crystals seized in the Republic of Korea.

15 Crystals seized in the United States of America.

16 Methamphetamine synthesized from synthetic ephedrine (shown for reference purposes).

Where numbers occur more than once, as in the case of 8 and 9, they indicate that those samples were seized on the same occasion.

Conclusion

The chemical characterization of drug samples can provide useful information for drug law enforcement, such as information regarding drug supply and distribution networks at the local, national, regional and international levels, and the methods and precursors used in clandestine drug production [17]. The similarities or differences among seized methamphetamine samples can give information on the links between suppliers and users for evidential purposes, and information about synthetic methods would be helpful in finding clandestine laboratories by monitoring trade not only in precursors, but also in key chemicals such as thionyl chloride and Pd-black, both of which are used as key chemicals when methamphetamine is produced by the Emde method.

In addition to the classical impurity profiling of methamphetamine by chromatographic methods, the use of carbon and nitrogen stable IRMS was investigated as a means of sample characterization. It was successfully shown that the origin of ephedrine and pseudoephedrine can be discriminated by IRMS and that this discrimination of the origin of the precursor is even possible from analysis of the end product, methamphetamine. Using these results, based on $\delta^{13}C$ and $\delta^{15}N$ values, it is clear that natural ephedrine was the main precursor for the crystalline methamphetamine seized in Japan.

The authors believe that stable isotope ratio analysis should prove particularly useful in cases where classical impurity profiling is of limited value, such as those of high purity samples, where the number and amount of manufacturing by-products is insufficient to draw operationally useful conclusions.

Indeed, in recent years, very pure samples of crystalline methamphetamine, suspected to have been produced by the Birch reduction method, mentioned in figure I, were seized in Canada and the United States. Some of those methamphetamine samples did not show marked differences in their impurity profiles and did not contain the two key impurities that would allow identification of the synthetic route (see figure II). The information on the values of $\delta^{13}C$ and $\delta^{15}N$ should be useful for the detailed discrimination of such methamphetamine samples.

Other potential targets for IRMS include norephedrine (phenylpropanolamine) and P-2-P. Recently, medical use of norephedrine has been discontinued because of serious side-effects. The increase in availability of *d*-pseudoephedrine, which is now widely used as a substitute for norephedrine for medical purposes, may also result in an increasing use of that substance in illicit methamphetamine synthesis.

As controls of ephedrine and pseudoephedrine are tightened and/or their availability becomes more limited, another precursor that may gain importance as a starting material for methamphetamine is P-2-P. When used for the illicit synthesis of methamphetamine, P-2-P will result in the racemic (50:50) mixture of *d*- and *l*-methamphetamine, which will have to be treated by chiral separation. Although this is a difficult procedure, the $\delta^{13}C$ and $\delta^{15}N$ ratios of methamphetamine synthesized from P-2-P should be investigated in the near future.

Another area of research relates to the identification of the geographical origin of *Ephedra* plants used for the manufacture of natural ephedrine. While the present article has shown that the origin of ephedrine and pseudoephedrine can be discriminated by carbon and nitrogen stable isotope ratio analysis, it is not yet possible to identify the growing area of *Ephedra* plants by means of $\delta^{13}C$ and $\delta^{15}N$ isotope ratio analysis. Hydrogen stable isotope analysis, which has proven useful for estimating the natal or breeding latitudes of migrating birds [18], may be an option. It may therefore become possible in the future to determine the origin of *Ephedra* plants used for the production of ephedrine and pseudoephedrine if a suitable database of the relationship between the growing area of *Ephedra* plants and the hydrogen stable isotope ratio becomes available.

The authors are seeking to obtain samples from pharmaceutical and other relevant companies worldwide for IRMS analysis and to collect information on manufacturing methods of current precursors. Comparison of the $\delta^{13}C$ and $\delta^{15}N$ values of an illicit sample with a database of values of legitimately manufactured precursors should then be useful to confirm the origin of precursors used in the manufacture of seized methamphetamine. It would also be helpful if the major exporting countries of ephedrine and pseudoephedrine provided data on licit trade and manufacturing methods.

Finally, since the value of stable isotope ratios is expressed as deviations from international standards (as δ notation expressed in units of parts per thousand), considerable care is necessary to obtain accurate results. Nevertheless, the authors hope that stable isotope ratio analysis will become a general analytical technique that can be applied throughout the world.

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