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# Methylamphetamine synthesis: Does an alteration in synthesis conditions affect the $\delta^{13}C$, $\delta^{15}N$ and $\delta^{2}H$ stable isotope ratio values of the product?

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**Conventional chemical profiling of methylamphetamine has long been employed by national forensic laboratories to determine the synthetic route and where possible the precursor chemicals used in its manufacture. This laboratory has been studying the use of stable isotope ratio mass spectrometry (IRMS) analysis as a complementary technique to conventional chemical profiling of fully synthetic illicit drugs such as methylamphetamine. As part of these investigations the stable carbon ($\delta^{13}C$), nitrogen ($\delta^{15}N$), and hydrogen ($\delta^{2}H$) isotope values in the precursor chemicals of ephedrine and pseudoephedrine and the resulting methylamphetamine end-products have been measured to determine the synthetic origins of methylamphetamine. In this study, results are presented for $\delta^{13}C$, $\delta^{15}N$, and $\delta^{2}H$ values in methylamphetamine synthesized from ephedrine and pseudoephedrine by two synthetic routes with varying experimental parameters. It was demonstrated that varying parameters, such as stoichiometry, reaction temperature, reaction time, and reaction pressure, had no effect on the $\delta^{13}C$, $\delta^{15}N$, and $\delta^{2}H$ isotope values of the final methylamphetamine product, within measurement uncertainty. Therefore the value of the IRMS technique in identifying the synthetic origin of precursors, such as ephedrine and pseudoephedrine, is not compromised by the potential variation in synthetic method that is expected from one batch to the next, especially in clandestine laboratories where manufacture can occur without stringent quality control of reactions.** 

**Keywords:** forensic science; stable isotope ratios; chemical profiling; isotope ratio mass spectrometry (IRMS); methylamphetamine.

## Introduction

In a previous paper[1] we described the $\delta^{13}C$, $\delta^{15}N$, and $\delta^{2}H$ values determined in methylamphetamine synthesized by reduction of the hydroxyl group in the benzylic position of either ephedrine or pseudoephedrine (Figure 1). The work dealt specifically with methylamphetamine produced from ephedrine or pseudoephedrine that was itself produced from either a natural source, i.e. extracted from the *ephedra* plant species, or from a semi-synthetic procedure based on fermentation processes that employ benzaldehyde, or from a fully synthetic source. The work demonstrated that by measuring $\delta^{13}C$, $\delta^{15}N$, and $\delta^{2}H$ isotope values, the synthetic source of the ephedrine or pseudoephedrine employed to make methylamphetamine may be determined. Makino *et al*. and Kurashima *et al*. have also demonstrated the same results.[2–4] Some commonly employed synthetic routes involving ephedrine and pseudoephedrine are shown in Figure 2. As part of the earlier work,[1] very carefully performed syntheses of methylamphetamine were carried out, employing natural and semi-synthetic ephedrine and pseudoephedrine. Each of the four synthetic routes shown in Figure 2 was used multiple times and every care was paid to ensuring that the synthesis parameters were consistent. The results of this work confirmed that methylamphetamine produced from a semi-synthetic source of ephedrine/pseudoephedrine will have a highly enriched $^{2}H$ content resulting in a positive $\delta^{2}H$ value, whereas methylamphetamine synthesized from a natural source of ephedrine/pseudoephedrine will have a negative $\delta^{2}H$ value. Similarly, the natural source of ephedrine/pseudoephedrine produces methylamphetamine with a more negative $\delta^{13}C$ value than does a semi-synthetic source of ephedrine/pseudoephedrine, supporting the findings of Makino *et al*.[3] and Kurashima *et al*.[2] Makino's research group also demonstrated that methylamphetamine from a fully synthetic source of ephedrine will have $\delta^{15}N$ values less than or equal to −10‰.[3]

However, the question arises whether carefully performed syntheses carried out in a research laboratory by synthetic chemists actually reflects what occurs in clandestine drug laboratories. It is unlikely that criminal enterprises pay too much attention to quality control or indeed even carefully monitor the course of chemical reactions. If random variations in reaction parameters such as stoichiometry, reaction time, reaction temperature, and reaction pressure occurs it is possible that stable isotope ratio values may be affected thereby rendering useless this comparatively new profiling technique. It is quite conceivable that within a single clandestine manufacturing facility, and even when following a single 'recipe', no two batches of methylamphetamine will be produced in a similar way. Conventional chemical profiling has been demonstrated to be most suitable for detecting subtle differences in chemical manufacturing byproducts and the organic impurity profile.[5–8] A gas chromatographic trace of

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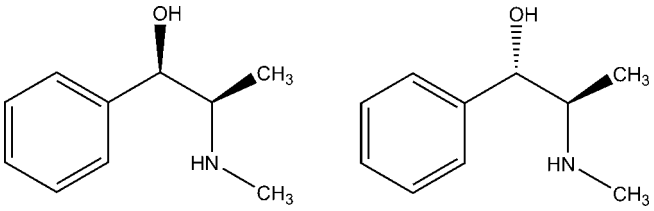


**Figure 1.** (1R,2S)-(−)-ephedrine and (1S,2S)-(+)-pseudoephedrine.

the methylamphetamine will usually reflect these changes. In the case of stable isotope ratio analysis, it is also conceivable that variations in synthesis conditions may alter stable isotope ratios to such an extent that they are no longer useful for strategic intelligence.

In this paper we describe work done at the NMI into preparing methylamphetamine from both a natural and semi-synthetic source of ephedrine/pseudoephedrine using the so-called 'Nagai' reaction[9–10] and 'Emde' reaction[11] (Figure 2). The Nagai reaction reduces the benzylic hydroxyl group in ephedrine with hydriodic acid and red phosphorus. The Emde reaction involves a two-stage process: the formation of the chloroephedrine intermediate followed by a reduction under reduced pressure to give methylamphetamine. Both sets of reactions were performed multiple times with variations of the reaction conditions built into the process to attempt to mimic typical variations that may be encountered in clandestine drug manufacturing facilities. Measurements of $\delta^{13}C$, $\delta^{15}N$, and $\delta^{2}H$ values were then made by Elemental Analysis (EA)/Thermal Conversion (TC)-Isotope Ratio Mass Spectrometry (IRMS). We also examine the $\delta^{13}C$, $\delta^{15}N$, and $\delta^{2}H$ values of methylamphetamine hydrochloride prepared from its base form via three different salting techniques.

Measurement uncertainty was determined for all our procedures for determining the stable isotope ratios of carbon, hydrogen, and nitrogen. This is important as it would be imprudent to draw conclusions relating to the synthetic origin of precursor chemicals based on small changes in stable isotope ratio values that are themselves less than the measurement uncertainty. It is particularly important to bear this in mind when using isotopic profiling to establish common origin or common batch.

## Experimental

### Reagents and chemicals

(1*S*,2*S*)-(+)-Pseudoephedrine hydrochloride (Product No. E2750, Lot. No. 125K1410, certified semi-synthetic origin, ≥99%), (1*R*,2*S*)-(−)-ephedrine hydrochloride (Product No. 862231, Batch 10620PH, certified semi-synthetic origin, ≥99%), (1*R*,2*S*)-(−)-ephedrine (Product No. 45285, Batch 350635, 99.7%), palladium 5 wt. % on barium sulfate reduced, red phosphorus and *N*-phenylbenzylamine (99%+) were obtained from Sigma-Aldrich (Castle Hill, NSW, Australia). Isopropanol and diethyl ether were obtained from Merck (Kilsyth, VIC, Australia). Analytical grade chloroform, dichloromethane and sodium acetate (anhydrous) were obtained from Mallinckrodt Chemicals (Philipsburg, NJ, USA). Hydrochloric acid (36%), sodium hydroxide pellets, sulfuric acid (98% *w/w*), glacial acetic acid and ammonia solution (28%) were obtained from UNIVAR Ajax Finechem (Seven Hills, NSW, Australia). Thionyl chloride was obtained from Riedel-deHaen (Seelze, Germany). Hydriodic acid was purchased from BDH Chemicals (Poole, England). All reagents were used without further purification. The certified reference material of methylamphetamine hydrochloride (NMI code D816b) was obtained from the reference collection of the National Measurement Institute, Australia (NMI). The internal standard solution employed for purity determination, was prepared by dissolving the appropriate amount of phenylbenzylamine in chloroform to give a final concentration of 800 µg/ml.

### Synthetic chemistry

*Synthesis of methylamphetamine via 'Nagai' route using a literature preparation*[9–10]

Ephedrine hydrochloride (or pseudoephedrine hydrochloride) (2 g), hydriodic acid (4.8 ml), and red phosphorus (0.7 g) were refluxed, between 125 °C and 135 °C, for 24 h and allowed to cool (this represented a molar ratio of HI: ephedrine of

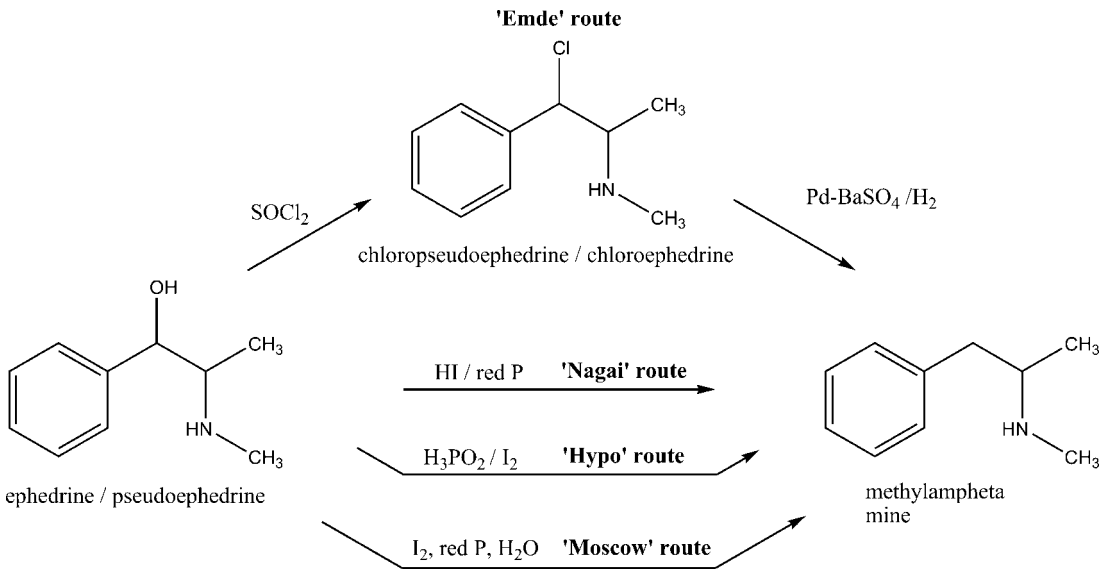


**Figure 2.** Common synthesis routes to methylamphetamine from ephedrine or pseudoephedrine.

5.4 : 1). The reaction mixture was filtered, diluted with water, and basified with dilute sodium hydroxide solution. The mixture was extracted with dichloromethane which was removed by rotary evaporation leaving an oil. The oil was dissolved in cold isopropanol, acidified with concentrated hydrochloric acid and diethyl ether added resulting in precipitation. The solid was filtered, washed with a mixture of isopropanol and diethyl ether and dried to give 1.4 g (76%) of white crystals, identified as methylamphetamine by comparison of gas chromatographic retention time and mass spectrum with a certified reference standard of methylamphetamine hydrochloride. Purity of the methylamphetamine hydrochloride was determined by gas chromatography fitted with a flame ionization detector (GC-FID).

*Variations to the Nagai literature preparation*

The synthesis described above was repeated four times with the following variations:

a. Ratio of hydriodic acid to ephedrine was changed from 5.4 : 1 to 1.9 : 1.
b. Reaction time changed from a reflux of 24 h to a reflux of 4 h.
c. Reaction temperature maintained at 160 °C to 170 °C.
d. Reaction temperature maintained at 90 °C to 100 °C.

*Synthesis of methylamphetamine via 'Emde'route using a literature preparation*

*Step 1: Synthesis of chloroephedrine*[11]. A solution of chloroform (15 ml) and thionyl chloride (10 ml) was chilled in an ice bath. To this was slowly added pseudoephedrine hydrochloride (or ephedrine hydrochloride) (10 g) and the mixture was stirred for six hours. Diethyl ether was then added resulting in precipitation of chloroephedrine hydrochloride (or chloropseudoephedrine). The product was washed with ether : chloroform (50 : 50) and dried yielding 9.8 g (90%) of chloroephedrine hydrochloride (or chloropseudoephedrine).

*Step 2: Synthesis of methylamphetamine*[11]. In a flask was added sodium acetate anhydrous (0.8 g) and water (11 ml). The mixture was made neutral with acetic acid. To this was added palladium on barium sulfate (1 g) and finally chloroephedrine hydrochloride (or chloropseudoephedrine hydrochloride) (2 g). The flask was attached to a Parr 3911 hydrogenation apparatus (Moline, IL, USA). The air was removed from the flask by vacuum pump and flushed with hydrogen several times and then charged with hydrogen to 30 psi. The flask was mechanically shaken till uptake of hydrogen ceased. The catalyst was filtered off and washed with water. The combined reaction mixture and aqueous washings were basified with dilute sodium hydroxide solution and the methylamphetamine base was extracted with dichloromethane. The dichloromethane was removed using a rotary evaporator leaving methylamphetamine base as an oil. The oil was dissolved in cooled isopropanol and acidified with concentrated hydrochloric acid. Diethyl ether was added resulting in precipitation of a crystalline material. The solid was filtered, washed with a mixture of isopropanol and diethyl ether and dried to give 1.4 g (83%) of white crystals, identified as methylamphetamine by comparison of gas chromatographic retention time and mass spectrum with a certified reference standard of methylamphetamine hydrochloride. The purity of the methylamphetamine hydrochloride was determined by gas chromatography-flame ionization detector (GC-FID).

*Variations to the Emde literature preparation*

The synthesis described above was repeated five times with the following variations:

a. The pressure of the reaction was changed from 30 psi to 15 psi.
b. The amount of catalyst employed was reduced from 0.8 g to 0.2 g.
c. The reaction time changed from 2 h under pressure to 6 h under pressure.
d. The reaction time changed from 2 h under pressure to 30 min under pressure.
e. A mixture of ethanol/methanol (2 : 1) was used as the solvent.

*Hydrochloride salt formation*

The following three procedures were used to convert methylamphetamine base, prepared as described earlier in the Synthetic chemistry section:

1. Methylamphetamine base was dissolved in acetone and hydrogen chloride gas was bubbled into the solution resulting in precipitation of methylamphetamine hydrochloride.
2. Methylamphetamine base was dissolved in cold isopropanol, acidified to pH 3 with concentrated hydrochloric acid and cold diethyl ether was added.
3. Methylamphetamine base was added to a solution of isopropanol, hydrochloric acid and diethyl ether and allowed to stand until precipitation of the hydrochloride occurred.

### Sample identification

The identity of the methylamphetamine was verified by gas chromatography-mass spectrometry (GC-MS) using the method of Anderson *et al.*[12–13] The methylamphetamine purity was determined using GVC-FID, as outlined in our previous work.[1]

### Stable isotope ratio mass spectrometry

Measurements of the stable isotope $\delta^{13}C$, $\delta^{15}N$, and $\delta^{2}H$ of the precursors and methylamphetamine products described here were determined using the IRMS methods described in our previous work.[1] Calibration and quality control of EA/TC-IRMS measurements is outlined in our previous work.[1]

The ability to determine isotopic fractionation patterns in the synthesis of methylamphetamine as being comparable or distinct is dependent on an estimation of measurement uncertainty. This was performed by combining bias and precision contributions using the square root of the sum of squares method[14] and as described in our earlier work.[1] For a 95% confidence interval ($k = 2$), an expanded uncertainty ($U$) for $\delta^{13}C$, $\delta^{15}N$, and $\delta^{2}H$ measurements was estimated to be ±0.4‰, ±0.5‰ and ±4‰, respectively. These uncertainty estimates were considered to be fit-for-purpose based on the range of values recorded for a high purity methylamphetamine HCl quality control analysed every five samples.

## Results and discussion

In our earlier work we demonstrated that multiple synthesis of methylamphetamine using the same reaction and precursor resulted in products having stable isotope $\delta^{13}C$, $\delta^{15}N$,

**Table 1.** $\delta^{13}C$, $\delta^{15}N$ and $\delta^{2}H$ values for Nagai synthesized methylamphetamine with changes to synthesis parameters

| | Methylamphetamine Product | | | | |
|---|---|---|---|---|---|
| Precursor | Reaction Synthesis Parameter Changed | Purity (%) | $\delta^{13}C_{VPDB}$ (±0.4‰)* | $\delta^{15}N_{Air}$ (±0.5‰)* | $\delta^{2}H_{VSMOW}$ (±4‰)* |
| Ephedrine* | Standard conditions as described in Synthetic Chemistry section | 95 | −25.6 | −0.4 | +133 |
| $\delta^{13}C = -25.6$‰ | Hydriodic acid : Ephedrine ratio (1.9 : 1) | 93 | −25.0 | −0.4 | +133 |
| $\delta^{15}N = -0.1$‰ | Reaction time = 4 h | 92 | −25.3 | −0.2 | +132 |
| $\delta^{2}H = +171$‰ | Reaction temperature (160 °C to 170 °C) | 95 | −24.9 | −0.2 | +140 |
| | Reaction temperature (90 °C to 100 °C) | 87 | −25.9 | −0.7 | +130 |
| Ephedrine* | Standard conditions as described in Synthetic Chemistry section | 96 | −29.6 | +2.5 | −172 |
| $\delta^{13}C = -29.4$‰ | Hydriodic acid : Ephedrine ratio (1.9 : 1) | 93 | −29.6 | +2.3 | −173 |
| $\delta^{15}N = +2.8$‰ | Reaction time = 4 h | 95 | −29.8 | +2.2 | −173 |
| $\delta^{2}H = -147$‰ | Reaction temperature (160 °C to 170 °C) | 85 | −29.1 | +2.4 | −168 |
| | Reaction temperature (90 °C to 100 °C) | 91 | −30.0 | +2.2 | −174 |

* Measurement uncertainty expressed as an expanded uncertainty at the 95% confidence interval.

and $\delta^{2}H$ values that were within measurement uncertainty of each other.[1] If the $\delta^{13}C$, $\delta^{15}N$, and $\delta^{2}H$ values are to be of value to forensic chemistry, then the isotopic profile of illegally produced methylamphetamine must remain within measurement uncertainty, even if the conditions under which the clandestine manufacture of methylamphetamine change.

Methylamphetamine was prepared multiple times, varying the reaction conditions, and the $\delta^{13}C$, $\delta^{15}N$, and $\delta^{2}H$ values were determined. Methylamphetamine was prepared from a semi-synthetic source of ephedrine by the so-called Nagai reaction five times, the first time using a synthetic procedure from the literature and the four subsequent occasions using variations of the original conditions, as outlined in the Experimental section. In each case the methylamphetamine product was isolated as the base, converted to the hydrochloride using a standard procedure as described in the Literature preparation section, and the carbon, nitrogen, and hydrogen stable isotope ratios were determined by EA/TC–IRMS. The results are presented in Table 1. These five syntheses were repeated using a natural source of ephedrine. The carbon, nitrogen and hydrogen stable isotope ratios for the methylamphetamine products are also shown in Table 1.

The results in Table 1 clearly demonstrate that the stable isotope ratios for carbon, nitrogen, and hydrogen are not affected, within measurement uncertainty, by changing synthesis conditions. In the first instance, the 'standard reaction condition' syntheses employed the method described by Skinner.[10] The $\delta^{13}C$ value of the methylamphetamine product was unchanged from the $\delta^{13}C$ value of the precursor ephedrine and the $\delta^{15}N$ values only slightly changed. The $\delta^{2}H$ value for the methylamphetamine product was substantially different from the $\delta^{2}H$ value of its precursor. This was not unexpected as the benzylic hydroxyl group in the ephedrine molecule is replaced with a hydrogen atom and the methylamphetamine has been isolated as the hydrochloride salt by the addition of an HCl group.

These results are also true for the methylamphetamine products which were prepared by the Nagai route with changes to certain reaction parameters (Table 1). The $\delta^{13}C$ value for each of the methylamphetamine products was the same within measurement uncertainty. Neither molar ratio, nor reaction time nor reaction temperature affected the $\delta^{13}C$ value. The same is also true of the $\delta^{15}N$ values. So, within the uncertainty of the method each $\delta^{13}C$ and $\delta^{15}N$ value was unchanged from the precursor ephedrine. This should not be surprising though, as neither the carbon skeleton nor the single nitrogen atom has undergone a chemical change during the reaction. These results are true for methylamphetamine samples prepared from a semi-synthetic source of ephedrine as well as methylamphetamine samples prepared from a natural source of ephedrine (Table 1).

The $\delta^{2}H$ values of each methylamphetamine products (Table 1), although depleted relative to the precursors, are the same within measurement uncertainty. The median of the five values (where a semi-synthetic ephedrine precursor was employed) is 133‰and with a measurement uncertainty for hydrogen of ±4‰ these values are equivalent. In other words, none of the deliberate changes in synthesis conditions affected $\delta^{2}H$ value of the product methylamphetamine. The median of the five values (where a natural ephedrine precursor was employed) is −173‰ and again these values all fall within measurement uncertainty showing that changes in synthesis conditions did not affect the $\delta^{2}H$ value of the product methylamphetamine. It is obvious too that after each synthetic variation, the $\delta^{2}H$ value, although depleted compared to the ephedrine precursor remains profoundly positive indicating the ephedrine precursor to be of a semi-synthetic source as indeed we knew it to be. These results are important because they demonstrate that the work highlighting the value of the $\delta^{2}H$ and $\delta^{13}C$ values[1–4] in determining the synthetic origin of the methylamphetamine precursors holds true even when changes are made to the synthetic conditions employed.

Methylamphetamine was also synthesized five times using the so-called Emde reaction, from a semi-synthetic source of pseudoephedrine. In the first case, the methylamphetamine was synthesized using a synthetic procedure from the literature, and the four subsequent occasions using variations of the original conditions. The carbon, nitrogen, and hydrogen stable isotope ratios of each of the methylamphetamine hydrochloride products are presented in Table 2. These five syntheses were repeated using a natural source of ephedrine, and the carbon, nitrogen and hydrogen stable isotope ratios for the methylamphetamine products are also shown in Table 2.

**Table 2.** $\delta^{13}C$, $\delta^{15}N$ and $\delta^{2}H$ values for Emde synthesized methylamphetamine with changes to synthesis parameters

| | | Methylamphetamine Product | | | |
|---|---|---|---|---|---|
| Precursor | Reaction Synthesis Parameter Changed | Purity (%) | $\delta^{13}C_{VPDB}$ (±0.4‰)* | $\delta^{15}N_{Air}$ (±0.5‰)* | $\delta^{2}H_{VSMOW}$ (±4‰)* |
| Pseudoephedrine* | No changes in synthesis parameters | 87 | −22.9 | +6.7 | +136 |
| $\delta^{13}C = -23.3$‰ | $H_2$ pressure reduced to 15 psi | 91 | −22.7 | +6.7 | +139 |
| $\delta^{15}N = +5.1$‰ | Reaction time = 0.5 h | 90 | −22.8 | +7.8 | +140 |
| $\delta^{2}H = +168$‰ | Reaction time = 6 h | 94 | −22.8 | +7.5 | +142 |
| Chloroephedrine* | $Pd/BaSO_4$ (0.2 g) | 97 | −22.8 | +12.3 | +132 |
| $\delta^{13}C = -22.5$‰ | | | | | |
| $\delta^{15}N = +5.2$‰ | | | | | |
| $\delta^{2}H = +186$‰ | | | | | |
| Ephedrine* | No changes in synthesis parameters | 92 | −29.2 | +2.7 | −155 |
| $\delta^{13}C = -29.4$‰ | $H_2$ pressure reduced to 15 psi | 90 | −29.4 | +3.3 | −153 |
| $\delta^{15}N = +2.8$‰ | Reaction time = 0.5 h | 90 | −29.2 | +2.6 | −148 |
| $\delta^{2}H = -147$‰ | Reaction time = 6 h | 88 | −29.3 | +3.0 | −150 |
| Chloropseudoephedrine* | $Pd/BaSO_4$ (0.2 g) | 93 | −29.7 | +2.8 | −155 |
| $\delta^{13}C = -29.6$‰ | | | | | |
| $\delta^{15}N = +2.8$‰ | | | | | |
| $\delta^{2}H = -139$‰ | | | | | |

* Measurement uncertainty expressed as an expanded uncertainty at the 95% confidence interval.

**Table 3.** $\delta^{13}C$, $\delta^{15}N$ and $\delta^{2}H$ values for Emde synthesized methylamphetamine using a different solvent

| | | Methylamphetamine Product | | | |
|---|---|---|---|---|---|
| Precursor | Reaction Synthesis Parameter Changed | Purity (%) | $\delta^{13}C_{VPDB}$ (±0.4‰)* | $\delta^{15}N_{Air}$ (±0.5‰)* | $\delta^{2}H_{VSMOW}$ (±4‰)* |
| Pseudoephedrine* | No changes in synthesis parameters | 87 | −22.9 | +6.7 | +136 |
| $\delta^{13}C = -23.3$‰ | Solvent = EtOH/MeOH | 93 | −22.6 | +7.5 | +151 |
| $\delta^{15}N = +5.1$‰ | | | | | |
| $\delta^{2}H = +168$‰ | | | | | |
| Chloroephedrine* | | | | | |
| $\delta^{13}C = -22.5$‰ | | | | | |
| $\delta^{15}N = +5.2$‰ | | | | | |
| $\delta^{2}H = +186$‰ | | | | | |
| Ephedrine* | No changes in synthesis parameters | 92 | −29.2 | +2.7 | −155 |
| $\delta^{13}C = -29.4$‰ | Solvent = EtOH/MeOH | 92 | −29.4 | +2.9 | −152 |
| $\delta^{15}N = +2.8$‰ | | | | | |
| $\delta^{2}H = -147$‰ | | | | | |
| Chloroephedrine* | | | | | |
| $\delta^{13}C = -29.6$‰ | | | | | |
| $\delta^{15}N = +2.8$‰ | | | | | |
| $\delta^{2}H = -139$‰ | | | | | |

* Measurement uncertainty expressed as an expanded uncertainty at the 95% confidence interval.

Once again it is observed that the methylamphetamine product obtained from each of the Emde synthetic variations has $\delta^{2}H$ values that are substantially changed from the $\delta^{2}H$ value of the precursor pseudoephedrine or ephedrine, due to the replacement of a benzylic hydroxyl group with a hydrogen atom as well as the methylamphetamine having been isolated as the hydrochloride salt by the addition of an HCl group. Similar to the results obtained for the Nagai experiments, the results show that changes in the synthesis conditions do not affect the $\delta^{2}H$ values of the product methylamphetamine within measurement uncertainty. While depletion has occurred, relative to the precursor, after each synthetic variation, the $\delta^{2}H$ value of the methylamphetamine products remains profoundly positive for methylamphetamine made using a semi-synthetic source of pseudoephedrine. Similarly, depletion has occurred for the methylamphetamine samples made from a natural source of ephedrine. The product methylamphetamine has a negative $\delta^{2}H$ value, as does its precursor ephedrine, again allowing for the assignment of the synthetic origin of the precursor. As observed for changes made to the 'Nagai' synthetic conditions, changes in the Emde synthetic conditions did not affect the ability to assign the synthetic origin of the precursors in methylamphetamine.

Table 3 shows the carbon, nitrogen and hydrogen isotope values of methylamphetamine prepared using the Emde reaction, however employing a different solvent. A mixture of

**Table 4.** $\delta^{13}C$, $\delta^{15}N$ and $\delta^{2}H$ values for synthesized methylamphetamine with changes to hydrochloride salt preparation technique

| | | Methylamphetamine Product | | | |
|---|---|---|---|---|---|
| Precursor | Reaction Synthesis Parameter Changed | Purity (%) | $\delta^{13}C_{VPDB}$ (±0.4‰)* | $\delta^{15}N_{Air}$ (±0.5‰)* | $\delta^{2}H_{VSMOW}$ (±4‰)* |
| Methylamphetamine base* | Salt type 1 | 95 | −23.1 | +5.3 | +111 |
| $\delta^{13}C = -23.2$‰ | Salt type 2 | 93 | −22.9 | +5.2 | +121 |
| $\delta^{15}N = +4.7$‰ | Salt type 3 | 94 | −23.0 | +5.1 | +128 |
| $\delta^{2}H = +98$‰ | | | | | |

* Measurement uncertainty expressed as an expanded uncertainty at the 95% confidence interval.

ethanol : methanol (2 : 1) was used in place of water. The $\delta^{2}H$ value of the methylamphetamine prepared from a semi-synthetic source of pseudoephedrine is somewhat enriched compared to the other Emde methylamphetamine products. While it is not certain what is causing this enrichment, a probable explanation is the contribution of the solvents. The noteworthy point however is that the $\delta^{2}H$ values still allow for the correct determination of the synthetic origin of the pseudoephedrine or ephedrine.

Converting the methylamphetamine base to the hydrochloride salt is an operation that will also affect the hydrogen stable isotope ratio. Table 4 presents results for three different methods of converting base to hydrochloride. Within measurement uncertainty, no change has occurred in either the $\delta^{13}C$ or $\delta^{15}N$ values. Salting techniques 1, 2, and 3 gave virtually the same results and there is very little difference also between these hydrochlorides and the base or the pseudoephedrine precursor ($\delta^{13}C = -23.3$‰, $\delta^{15}N = +5.1$‰, $\delta^{2}H = +168$‰). The $\delta^{2}H$ values, however, do vary. As one would expect adding an HCl moiety to the molecule will obviously alter the value from that of the methylamphetamine base. But there is also a difference of $\geq$10‰ between the hydrochloride salts generated by the salting technique 1 (gaseous HCl) and salting techniques 2 and 3. A difference of 10‰exceeds the measurement uncertainty for hydrogen of ±4‰. However, this difference is not sufficiently large to compromise the value of the hydrogen stable isotope ratio in determining the synthetic origin of the methylamphetamine precursors, ephedrine and pseudoephedrine as described in our earlier work[1] and the work of Makino *et al.*[2–4] Importantly, all the $\delta^{2}H$ values are still profoundly positive.

## Conclusions

The results presented in this paper demonstrate that the stable isotope ratios of carbon, hydrogen, and nitrogen in methylamphetamine produced by either the Nagai or Emde routes are not affected by changes to synthetic conditions within the measurement uncertainty of the experiments. The carbon and nitrogen stable isotope ratios of the product methylamphetamine were unchanged from the ratios in the precursor pseudoephedrine and ephedrine. The hydrogen stable isotope ratios varied from those of the precursor but only because a hydroxy group was replaced with a hydrogen atom. The hydrogen stable isotope ratios of each of the methylamphetamine products were the same within measurement uncertainty and independent of changing synthetic conditions. This is important as it means that stable isotopic profiling may be used to determine the synthetic origin of the ephedrine and pseudoephedrine precursor chemicals. Changes to the way in which the hydrochloride salt of methylamphetamine is prepared can clearly affect the hydrogen stable isotope value. Changes to the reaction solvents can affect the hydrogen stable isotope values; however, these experiments are only preliminary and require further investigation. What is clear and important for this study, is that none of these possible variations appear to compromise the value of isotopic profiling in determining the synthetic origin of the precursor chemicals, ephedrine, and pseudoephedrine.

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