Forensic Science International: Synergy 2 (2020) 194–205

Contents lists available at ScienceDirect

Forensic Science International: Synergy

journal homepage: https://www.journals.elsevier.com/forensic-science-international-synergy/

A review of the newly identified impurity profiles in methamphetamine seizures

Isaac Onoka [a, *], Andrew Toyi Banyika [a], Protibha Nath Banerjee [a], John J. Makangara [a], Laurence Dujourdy [b]

[a] Department of Chemistry, College of Natural and Mathematical Sciences, University of Dodoma, P.O Box 259, Dodoma, Tanzania
[b] Agrosup Dijon, Department of Engineering and Process Science, Research Support Service Agrosup Dijon - DSIP - Bât. Longelles 26 bd Dr Petitjean, BP 87999 21079, Dijon Cedex, France

ARTICLE INFO

Article history:
Received 1 May 2020
Received in revised form
21 June 2020
Accepted 22 June 2020
Available online 24 June 2020

Keywords:
Methamphetamine
Impurity profiles
Stable isotopes
Synthetic route

ABSTRACT

Forensic intelligence of synthetic illicit drugs suffers a problem of continuous introduction of new synthetic methods, modification of the existing routes of manufacture, and adulterations practiced by criminal networks. Impurity profiling has been indispensable in methamphetamine intelligence based on precursors, synthetic routes, and chemical modifications during trafficking. Law enforcement authorities maintain the credibility and integrity of intelligence information through constant monitoring of the chemical signatures in the illicit drug market.

Changes in the synthetic pattern result in new impurity profiles that are important in keeping valuable intelligence information on clandestine laboratories, new synthetic routes, trafficking patterns, and geographical sources of illicit Methamphetamine.

This review presents a critical analysis of the methamphetamine impurity profiles and more specifically, profiling based on impurity profiles from Leuckart, Reductive amination, Moscow, Emde, Nagai, Birch, Moscow route; a recent nitrostyrene route and stable isotope signatures. It also highlights the discrimination of ephedrine from pseudoephedrine sources and the emerging methamphetamine profiling based on stable isotopes.

1. Introduction

Methamphetamine is a schedule II controlled substance according to the Single Convention on Narcotic drugs [1] and the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988 [2]. It is highly addictive drug with a potent central nervous system (CNS) stimulant properties [3,4]. The United Nations Office on Drugs and Crime (UNODC) report MA as the most abused drugs worldwide [3,5,6]. For the last two decades, the use of MA has been increasing in many countries worldwide [3,6–10]. In Japan, about 15,000 drug arrests were from cases related to MA [11] accounting for 90% of all reported violations [12]. Previous studies have documented the prevalence of methamphetamine over other synthetic drugs elsewhere [13,14].

The impurity profiling of MA provides the linkage of illicit drug seizures based on the chemical signatures contained in the seized illicit drugs [15–17]. The method uses organic and inorganic impurities which are by-products of reactions in the final formulation of MA. It has successfully been used to establish intelligence information in France [18,19], Australia [20,21], Thailand [22,23], China [24], Philipines [25], Japan [22,26,27], USA [28], Spain [29], Korea [30,31] and in many other places worldwide [7,19,32–35]. Recently, the emerging complementary profiling method based on stable isotopes has drawn the interest of many researchers [36–38]; its details will be included in this review.

The chemical analysis of illegal drugs provides valuable information about the conspiracy links and trafficking routes, categorizing the seizures based on the signatures, thereby identifying their origins [39,40]. As a complementary law enforcement investigative work, it provides a background intelligence information concerning the number of sources of drugs, whether those sources are within a country or are internationally based and also unveiling the points of distribution and distribution networks. Similarly, the impurity profiles identifies the emergence of new clandestine laboratories and their associated synthetic methods, which, in turn,

* Corresponding author.
E-mail address: isaac.onoka@udom.ac.tz (I. Onoka).

https://doi.org/10.1016/j.fsisyn.2020.06.004

provides background intelligence information [41]. Chemical profiling marks the principal purpose of the intelligence of illicit drugs by establishing a link between the clandestine laboratories, suppliers, and users. The chemical information obtained from a drug can indicate its synthetic method, adulterations during trafficking, and the operations of the criminal networks [42].

Generally, the fundermental role of a forensic chemist in drug profiling is extract the chemical signatures that can be used to establish the degree of commonality of seizures with their origins or a specific group of other samples [6,43] as well as linking the signatures with the possible synthetic methods, conditions, and post-production modifications. A comprehensive examination and comparison of the chemical signatures has found a growing application strategically at the macro level [6] and tactically at the micro-level [35]. These advances have helped the police and criminal investigators at both national and global scales to establish the dynamics of illicit drug markets, locate the drug traffickers, establish conspiracies links between dealers and users [11,43,44].

In this decade, extensive number of research studies on the chemical profiling of MA and its derivatives are focusing on the determination of organic and inorganic impurities [19,45], determination of synthetic routes [46], synthesis of the impurities [17,46] identification of the impurities [17,39,40] concentration in body fluids [47] characterization [48] and the extraction and separations of the impurities [49,50].

In this paper, we critically analyze the impurity profiles of MA synthesized from ephedrine, pseudoephedrine, and 1-phenyl-2-propanone (P2P) precursors and subsequently analyze their potential use for intelligence perspective.

1.1. The synthetic schemes of methamphetamine and the specific-route impurities

The Forensic intelligence of illicit drugs is an exciting subject and very challenging. In totality, it embraces the determination, identification, and characterization of the individual components in the final formulation of illicit drugs regarded in this review as the impurities, intermediates, and the contaminants. Depending on the level of operation of a clandestine laboratory, an illegal drug is an assemblage of constituents carrying the information about the synthetic route [16,32], condition-specifics [19], reagents [30], adulterations during trafficking, synthetic batches and sometimes the chemical process level of the cooks (purity) [40,51].

Like in any other reaction, each synthetic scheme has by-products emanating from the conversion of the precursors to MA. For instance, some constituents are by-products of the reaction conditions; others are formed from the conversion of precursors to intermediates and from intermediates to MA while others are intentionally added as cutting agents for potency or weight [52] and as artifacts described by Broséus et al. [53]. Therefore, the final formulation of MA is charceterized by a variation of the relative abundance of the major by-products, intermediates, and impurities that defines a chemical signature.

Although different MA seizures produced from the same precursor, using similar route and the same reagents have related impurity profiles; some intra and inter batch variations may still occur due to varying reaction conditions. This variation is essential to distinguish chemists (cooks) by attaching a specific profile to reaction conditions practiced by a particular clandestine laboratory.

Based on a certain probability of a link corresponding to the calculation of a threshold, two or more exhibits will have the same chemical profiles supporting the fact that they originate from the same batch, with the strength of support increasing as profiles become more complex [54]. Otherwise, a range not meeting the threshold can only distinguish the samples rather than discriminating against their cooks.

For quite a long time, the clandestine synthesis of MA employs three major precursors, namely ephedrine, pseudoephedrine, and the 1-phenyl-2-propanone (P2P) [55–59]. With P2P (Fig. 1), the Leuckart route (VI) and reductive amination are the most commonly used routes for the synthesis of MA [48,60]. In contrast, ephedrine/pseudoephedrine precursors (Fig. 2) convert to MA through the Nagai (I) [52,61], Emde (II) [52,61], Hypo (III) [62], Moscow (IV) [63] Rosenmund (V) [64,65] and Birch/Nazi (VI) pathways [66,67].

As one of the main MA precursors, P2P reaction scheme involves the reductive amination reactions Fig. 1 (I–V) and the Leuckart (HCL/H_2O). The reductive amination reaction of P2P to MA is achieved through $Pd/H_2/NH_2CH_3$, $NaBH_4/NH_2CH_3$, $NaBH_3CN/NH_2CH_3$, HCl/H_2O, $Pt/H_2/NH_2CH_3$, and $Hg/Al/NH_2CH_3$, however, the aluminum/mercury (Al/Hg) amalgam in a slightly acidic media method is reported to be the most commonly used method in Europe and USA [48]. Although the method has long history, 1-phenyl-2-propanol formed from the direct reduction the precursor, P2P, remains the potential intelligence impurity profile [48,68].

Described by Verweij in 1989 [68], the Leuckart route (Fig. 1VI) is achieved by the addition of *N*-methylformamide, methylamine or formic acid followed by H_2SO_4 or HCl to form MA. By means of *N*-methylformamide, the reaction result in a Leuckart route determinant; the *N*-formylmethamphetamine disputed by Qi et al. [20] and Barron et al. [69]; and non-synthetic route determinants namely dibenzylketone, *R*-benzyl-*N*-methylphenethylamine, and *N*-methyldiphenethylamine [70]. The synthetic-route character of *N*-formylmethamphetamine argumented by Barron et al. and Qi et al. was resolved by the identification of α,α'-dimethyldiphenethylamine and *N*, α,α'-trimethyldiphenethylamine by Barron et al. The two impurities were later confirmed by Vanitha et al. [48] having identified them in Leuckart based MAs only.

The Nagai route (Fig. 2(I)) is associated with the formation of (2*E*)-*N*-methyl-3-phenyl-*N*-(1-phenylpropan-2-yl)prop-2-enamide, iodoephedrine, *N*-methyl-*N*-(α-methylphenyl)amino-1-phenyl-2-propanone and (*Z*)-*N*-methyl-*N*-(α-methylphenylethyl)-3-phenylpropanamide [65,71].The impurities are formed from the nucleophilic substitution reaction of $-OH$ group of ephedrine/pseudoephedrine to form idoephedrine or iodopseudoephedrine. The intermediary iodine is liable to internal nucleophilic attack from the adjacent nitrogen to form *cis*- and *trans*-1,2-dimethyl-3-phenylaziridines which is reduced to MA or hydrolysed to P2P [72]. In a prolonged acidic conditions, the latter undergo condensation to form 1,3-dimethyl-2-phenylnaphthalene and 1-benzyl-3-methylnaphthalene reported to be the specific synthetic route signatures [73,74].

The conversion of ephedrine/pseudoephedrine to MA via Emde route is the dominant synthetic route in the South East Asia [73]. In contrast to the Nagai route, the Emde reaction scheme is augmented by S_N1 substitution (intramolecular nucleophilic displacement) or S_N2 substitution (intermolecular displacement) of the $-OH$ in ephedrine/pseudoephedrine with chloride to form a racemic mixture of (+)-chloropseudoephedrine and (-)-chloroephedrine of variable impurity concentrations [75,76]. The (+)-chloropseudoephedrine and (-)-chloroephedrine can then undergo a cyclic ring closure to form *cis*-1,2-dimethyl-3-phenylaziridines and *trans*-1,2-dimethyl-3-phenylaziridines, respectively. Accordingly, (+)-norpseudoephedrine and (-)-norephedrine alternative precursors undergo similar reaction to form (+)-chloromethylpseudoephedrine and (-)-chloromethylephedrine. These intermediates may eliminate the HCl to form 1-propenylbenzene and 2-propenylbenzene or can undergo a rearrangement to form 1-dimethylamino-1-phenyl-2-chloropropane [77]. The route specific potential of the intermediary aziridines

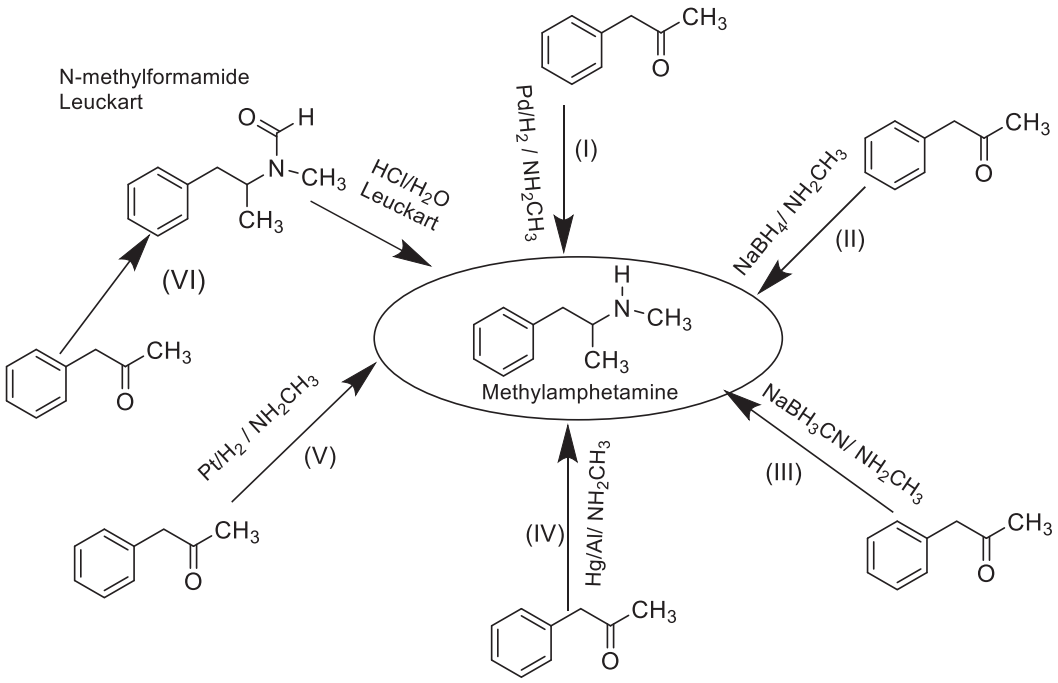

Fig. 1. Synthesis of MA from P2P routes: (I) $Pd/H_2/NH_2CH_3$, (II) $NaBH_4/NH_2CH_3$, (III) $NaBH_3CN/NH_2CH_3$, (IV) $Hg/Al/NH_2CH_3$, (V) $Pt/H_2/NH_2CH_3$ (VI) HCl/H_2O.

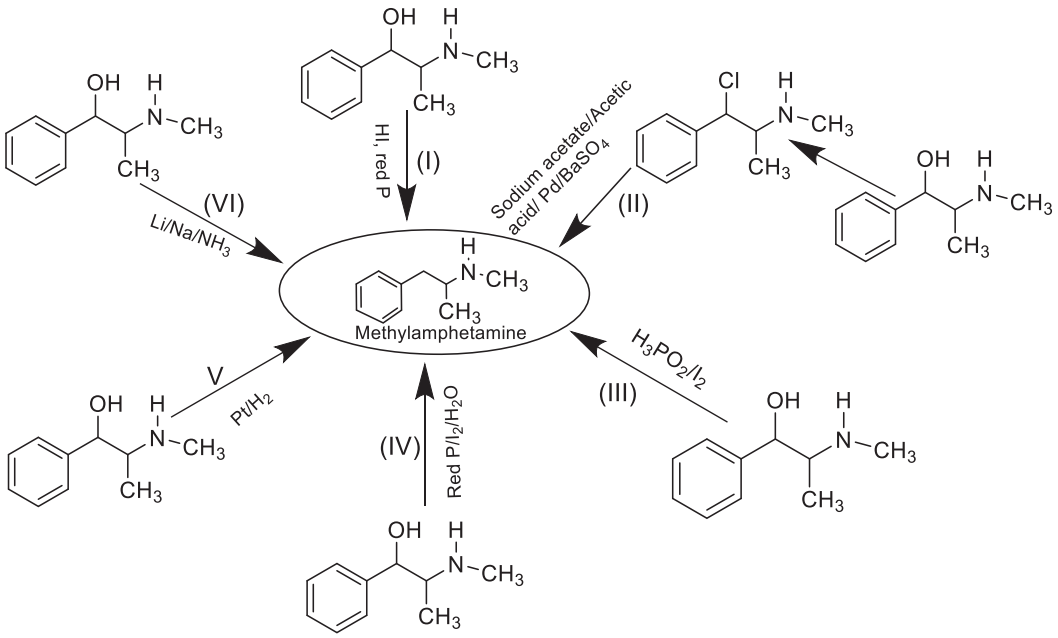

Fig. 2. Ephredine/Pseudoephredine synthetic routes: (I) Nagai route, (II) Emde route, (III) Hypo route, (IV) Moscow route (V) Rosenmund and (VI) Nazi/Birch route.

was contradicted by Ko et al. [37] and Salouros et al. [59] having identified 1-methylamino-1-phenyl-2-chloropropane as a vapour-phase nucleophilic product of the aziridine and *N*-methyl-1-(4-[2-(methylamino)propyl]phenyl)-1-phenylpropan-2-amine. The latter was recogonized in "Moscow" and Nagai related methods and could not qualify as a route specific impurity for Emde route [63,78]. Ko et al. instead identified and proposed 1-methylamino-1-phenyl-2-chloropropane (chloroephedrine/chloropseudoephedrine as route specific impurity for the Emde method. Other non-route specific impurities include methyephedrine, *N*-formylephedrine, *N*-acetylephedrine, *N,O*-diacetylephedrine and *N*-acetylamphetamine.

"Moscow" method Fig. 2(IV) is achieved by a reaction between ephedrine/pseudoephedrine with red phosphorus and iodine in water [59]. Its mechanism is treasured in the regenerative role of red phosphorus [79]. Skinner [73] as supported by NicDaéid et al. [45] proposed a scheme based on the oxidation of P by I_2 to diphosphorus tetraiodide (P_2I_4) followed by the decomposition of P_2I_4 in water to form phosphoric acid and phosphonium iodide. The mixture them converts to hydroiodic acid (HI) and phosphine (PH_3)

upon heating. The former protonates the −*OH* of ephedrine/pseudoephedrine to form aziridine intermediates which potentially reduce to MA as in the case of the Nagai route [73].

Birch/Nazi route (Fig. 2 (VI)) is a reduction reaction of ephedrine/psedoephedrine using excess alkali metal e.g., lithium/sodium in liquid ammonia to form 1-(1′,4′-cyclohexadienyl)-2-methylaminopropane (CMP) [54], notated as (*S*)–*N*-Methyl-1-(1,4-cyclohexadienyl)-2-propanamine [66]. The impurity is the most commonly encountered MA impurity prepared by the Birch route. Its reaction scheme is based on the role of alkali metals preferably lithium as a proton source for the −*OH* of ephedrine/pseudoephedrine. As lithium protonates the precursor, NH_3 facilitate the reduction of the aromatic rings to form 1-(1,4-cyclohexadienyl)-2-methylaminopropane [80]. This primary impurity associated with the lithium - ammonia method normally results in high CMP:MA ratio limiting the isolation of the impurity. Martinez et al. [81] proposed potassium permanganate and aquous base for effective CMP isolation.

1.2. A paradigm shift in methamphetamine precursor production

As a result of the crackdown measures taken against the production, trafficking and the availability of the P2P and ephedrine/pesudoephedrine, access to the precursors has shifted to the illicit manufacture of the precursors through readily available starting materials with new routes leading to the emergence of new impurity profiles [82–84].

For quite a long time, the synthesis of phenyl-2-propanone is through a vast number of starting materials such as α-phenylacetoacetonitrile [83,84], α-phenyl-β-methyleneglycol [85], α-phenylisopropyl alcohol [86] phenylacylmalonic ester [87] phenylacetyl chloride [88] α-methylstyrene with thallium nitrate, and benzene via o,o-diprotonated nitro olefin [89], β-methyl-β-*N*itrostyrene, and phenylacetic acid (PAA).

Although several P2P synthetic schemes were available in the 1980s, the illicit production of P2P was mainly through Phenylacetic acid (PAA) via acetic anhydride and lead (II) acetate; and β-methyl-β-*N*itrostyrene via Fe/H^+ [65].

A recent twist in the production of P2P has recently involved the nitrostyrene method (NTS) [82]. This emerging synthetic scheme results in nitrostyrene recently identified in MA samples seized in Mexico [55] and the USA [82]. The NTS method uses benzaldehyde and nitroethane in Knoevenagel reaction to form a nitrostyrene, yellow solid, which converts to P2P in the presence of iron powder and hydrochloric acid [82–90].

The evolution of the P2P clandestine chemistry is further confirmed by the re-emergence of a new impurity profile in place of α-benzyl-*N*-methylphenethylamine and *trans*-*N*-methyl-4-methyl-5-phenyl-4-penten-2-amine from the usual foul-smelting of a crystalline PAA [82]. The synthesis of P2P from PAA (Fig. 3 (a)) utilizes the then easily available ethyl phenylacetate (EtPA). However, a recent decline of EtPA and its associated esters and amides resulted in a shift in the P2P precursors (Fig. 3(b)) resulting in the emergence of new characteristic impurities recently reported in the in Australia [91] and observed in the USA [82].

The P2P produced from the PAA method and nitrostyrene (NTS) convert to MA with route-specific markers intelligently used to trace the sources of P2P.

The dynamics of the operations of criminal MA networks is one of the exciting profiling topics appealing to close monitoring by intelligence agencies. A recent Drug Enforcement Administration (DEA) MA Profiling Program (MPP) done in the USA [82,92] recorded trade-off impurity profiles assigned to pseudoephedrine route to those assigned to P2P precursors. According to the MA impurity profiles documented by this program, the impurity profiles derived from pseudoephedrine decreased significantly since 2007 with increasing impurity profiles derived from P2P. This shift was associated with a spike in unknown synthetic route assignments and a sharp decrease (84%) in samples assigned to a P2P-based recipe in the first quarter of 2015 [82,91].

1.3. The emerging methamphetamine impurity profiles

In response to the crackdown measures imposed on the production and trafficking of MA and its precursor chemicals, clandestine laboratories circumvent the law enforcement authorities by deriving the precursors from uncontrolled substances such as phenyl acetic Acid (PAA) [40], nitrostyren [82], and legal medicine [93] resulting into the emergence of new impurity profiles.

The emergence of impurity profiles such as dimethylamphetamine and *p*-methoxyamphetamine was recently documented by Stojanovska et al. [54] and supported by a literature collection of impurity profiles and synthetic route of manufacture of methylamphetamine, 3,4-methylenedioxymethylamphetamine, amphetamine, dimethylamphetamine, and *p*-methoxyamphetamine as well as the recently identified less potent *l*-methamphetamine in place of *d*-methamphetamine in the United States [57].

Since their identification in seized MA, several MA impurity profiling [19,53,76,91] reveal profiles that are potentially important for strategic, tactical and operational intelligence of MA in the USA [57], France [18] Australia [20,44,94–96] Korea [30], Iran [97], China [24], Philipines [25], Japan [98] and Thailand [22].

1.3.1. Impurities from metal catalytic hydrogenation

Metal catalytic hydrogenation of ephedrine/pseudoephedrine and P2P is one of the oldest MA synthetic methods [35,40,99–101]. Using ephedrine/pseudoephedrine, the clandestine laboratories often use palladium via the Rosenmund route [101], lithium/NH_3 via Birch route, and nickel via Emde route [100]. The reaction involves the reduction of the C-X (X-halo, phosphate, and sulfate) (Fig. 4) rather than the benzylic OH group to form methamphetamine [100].

Using P2P, an imine intermediate MA base is formed from a reaction of between P2P with methylamine. The MA freebase is then distilled and directly converted to hydrochloride salt [99,100]. Fig. 5 represents a reductive amination for the conversion of P2P to MA hydrochloride.

Reaction (c) occurs through heterogeneous reactions with internal or external sources of hydrogen in the presence of Pd, Pd/C, Pd/BaSO4, Pt, Pt/C, CuO, CaSO4, BaSO4, Raney Nickel (Ni-Al) [100]. Tracking the traces of metals in the final formulation of MA has been used to determine the synthetic routes. MA manufactured from ephedrine/pseudoephedrine through the Emde and Nagai methods was found to contain *N*-methyl-1-{4-[2-(methylamino) propyl]phenyl}-1-phenylpropan-2-amine and (1*S*,2*S*)-1-methylamino-1-phenyl-2-chloropropane as route-specific impurities [61]. Since their identification, they have been used as Emde route-specific signatures [61,76,77].

Furthermore, (1*S*,2*S*)-1-methylamino-1-phenyl-2-chloropropane has recently been used as an additional route-specific marker impurity synthesized from ephedrine via chloroephedrine by the Emde route (Fig. 6) [64]. The metal catalysis reaction of (1*R*, 2*S*)-(+)-ephedrine or (1*S*, 2*S*)-(+)-pseudoephedrine results in the formation of chloroephedrine/chloropseudoephedrine which is hydrogenated to (*S*)-(+)-Methamphetamine.

Recent profiling of reductive amination of P2P made from PAA/lead (II) based MA [102] elucidated *trans*-*N*-methyl-4-methyl-5-phenyl-4-penten-2-amine and α-benzyl-*N*-methylphenethylamine. *Trans*-*N*-methyl-4-methyl-5-phenyl-4-penten-2-amine used as a route-specific marker was presumed acetone and P2P

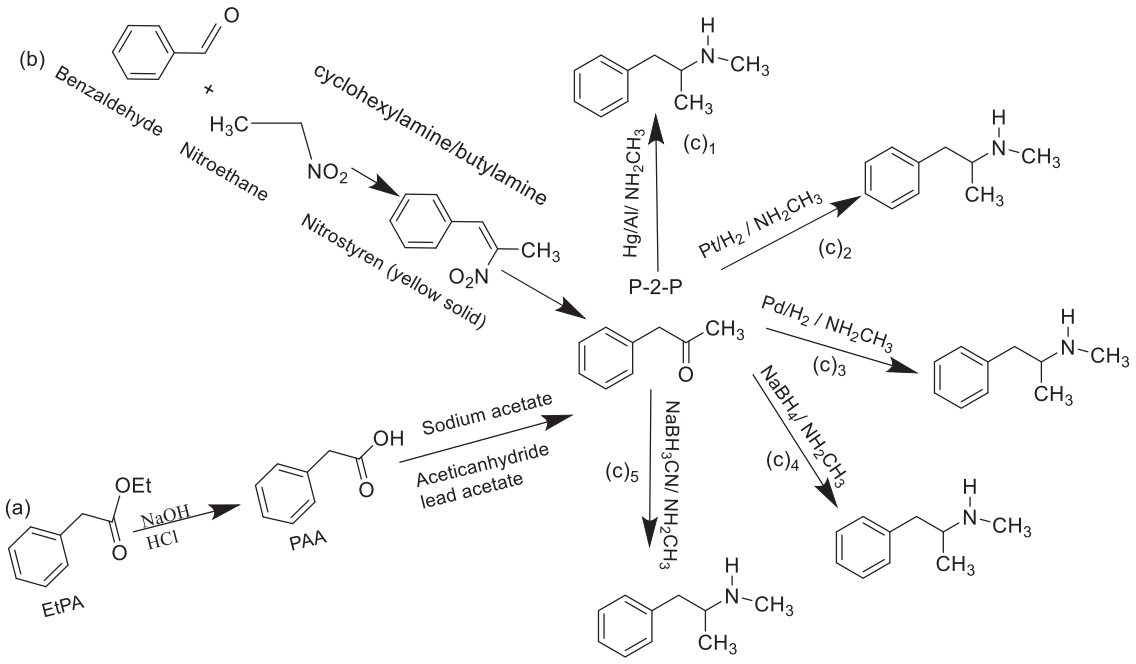

Fig. 3. A paradigm shift in MA precursor production: (a) PAA method,(b) nitrostyrene (NTS) method (c) 1–5 synthetic routes of P2P to MA.

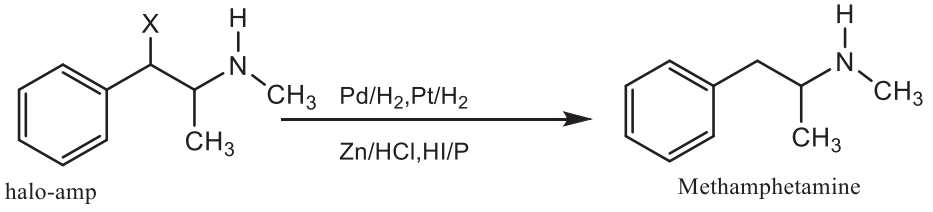

Fig. 4. C-X reduction to form MA: X = Cl^-, SO_4^{-2}, H_2PO_4, and ClO_4.

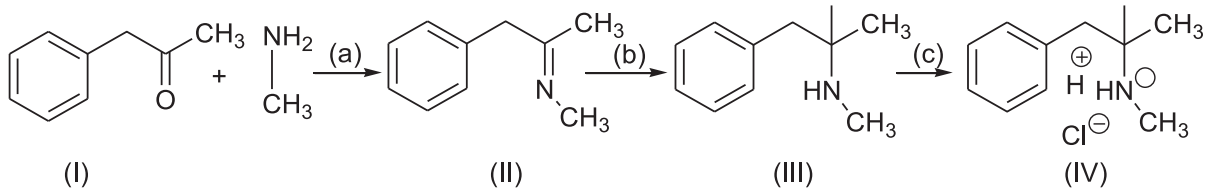

Fig. 5. Imine reduction to Methamphetamine: (I) P2P, (II) Methylamine, (III) Phenyl acetone methylimine (IV), Methamphetamine freebase, (V) Methamphetamine hydrochloride salt. (a) Removal of water, (b) reduction of imine to amine, (c) addition of hydrogen chloride.

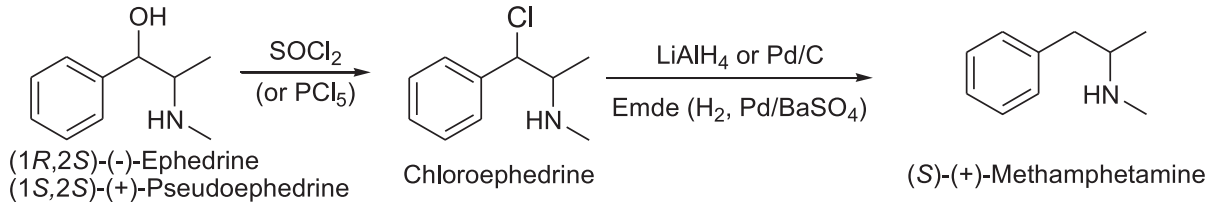

Fig. 6. Metal catalytic reduction of (1*R*, 2*S*)-(+)-ephedrine or (1*S*, 2*S*)-(+)-pseudoephedrine.

condensation product, however, this assumption could not explain why the little amount of the impurity and its associated intermediates produced even if the P2P was refluxed in acetone for a long time.

Furthermore, an attempt to produce P2P using a Dakin-West and lead (II) acetate conditions [102] were futile and could not yield the expected *trans*-*N*-methyl-4-methyl-5-phenyl-4-penten-2-amine as an impurity.

The best reasoning so far centers the argument on the role of a low-level 4-carbon acetate unit as an intermediate. Since acetic acid undergoes decarboxylation in aqueous solution over a range of temperatures, a route-specific marker impurity, *trans*-*N*-methyl-4-methyl-5-phenyl-4-penten-2-amine results from an intramolecular reaction of lead acetate with P2P via chelation controlled transition states followed by decarboxylation [102,103]. Fig. 7 shows the proposed mechanism for the formation of this route-specific marker.

The reductive amination of P2P is also associated with the formation of α-benzyl-*N*-methylphenethylamine as a synthetic route characteristic impurity. The MPP identified the contaminant at the DEA's Special Testing and Research Laboratory [102].

The emergence of new impurity profiles in MA analysis suggests, possibly, a change in the synthetic route parameters or the synthesis of precursor chemicals. The foul-smelting of a crystalline PAA results in new impurity profiles monitored in seized MA samples. The impurities associated with the modified P2P synthetic pathway are α-benzyl-*N*-methylphenethylamine and *trans*-*N*-methyl-4-methyl-5-phenyl-4-penten-2-amine) [82]. They have been used to track MA synthesized from PAA.

The emergence of *N*-butylamphetamine and *N*-cyclohexylamphetamine in seized MA has recently triggered the nitroalkene chemistry. The two impurities result from a Knoevenagel reaction of benzaldehyde and nitroethane to form a nitrostyrene [90].

Toske et al. [82] referred to this method as a nitrostyrene method (NTS) or a nitropropene method. The catalytic activities of butylamine/cyclohexylamine influence the conversion of the P2P precursors. The catalysts react with benzaldehyde to form imine, which then reacts with the nitroalkane to form a nitrostyrene as an intermediate [82]. The reaction mixture at this step contains nitrostyrene and extractable cyclohexylamine/butylamine with a significant reaction potential. Based on a reaction proposed by Hass et al. [90], nitrostyrene converts to P2P in the presence of iron powder and hydrochloric acid. The extractable cyclohexylamine/butylamine can then react with P2P to form the stable *N*-butylamphetamine, and *N*-cyclohexylamphetamine elucidated in MA seizures. Fig. 8(a) and (b) represents the formation of *N*-butylamphetamine and *N*-cyclohexylamphetamine.

Since 2015, the two impurities were detected in MA seizures collected in the USA [82]. The identification of the two impurities has been fundamental in tracking the P2P based MA synthesized by the nitrostyrene chemistry.

1.3.2. *Emerging impurity profiles from pharmaceutical compounds*

In response to the crackdown measures taken against controlled substances, ephedrine, and pseudoephedrine, other adaptation strategies used by clandestine laboratories are co-ingredients of legal medicines, direct extraction from *ephedra* plants [77,93,103,104] as well as direct synthesis from easily available starting materials [83,84]. Although Lee et al. [31] reports less common MA crystals containing pharmaceutical impurities, Barker and Antia [77] had a different opinion on the most common sources of ephedrine and pseudoephedrine used to synthesize crystal MA. The latter as supported by Liu et al. [93] who also considered medicinal drugs as the most common sources of pseudoephedrine and ephedrine.

Synthesis from legal medicines is the most common coping strategy practiced by clandestine laboratories to avoid strict measures from the law enforcement authorities [77]. The legal medicines approach result in MA whose final formulation contains pharmaceutical signatures that used to reflect the trends in precursor chemicals, manufacturing sources, and the trafficking patterns organized by the criminal networks. Unlike by-products, there is limited literature linking pharmaceutical impurities to the synthetic route of MA.

More recently, the MA profiling based on synthetic pharmaceutical signatures has been done in Korea [31], Iran [97], China [24], Japan [98] and Thailand [22]. several studies have been done in this field, more research is required to unveil the potential of pharmaceutical impurities beyond their existence as sole impurities into the final MA formulations. Tracking the by-products down to their origin and their point of entry may provide the potential of establishing synthetic routes using pharmaceutical contaminants.

In a profiling program conducted in Korea between 2006 and 2011, Acetaminophen, Caffeine, Phenacetin, Ambroxol, Chlorpheniramine, Desloratadine, Barbital, Ketamine, Procaine, and Dimethylsulfone were elucidated as characteristic pharmaceutical impurities [31]. The profiling program linked these impurities with cold medicines, cold relievers, ingredients of analgesic drugs [105], expectorant, and dietary supplements extracted together with ephedrine/pseudoephedrine. In contrast, others added as

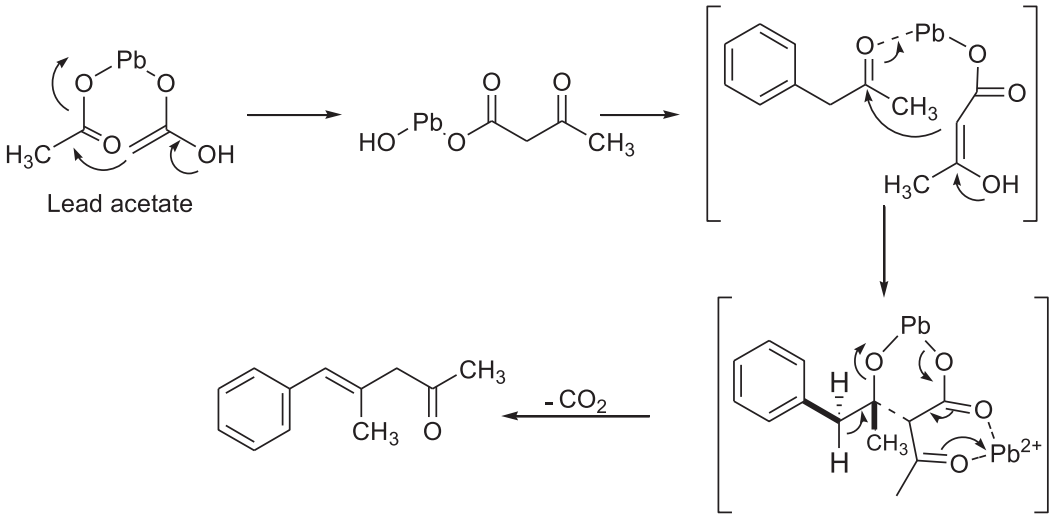

Fig. 7. The reaction mechanism for the formation of *trans*-*N*-methyl-4-methyl-5-phenyl-4-penten-2-amine.

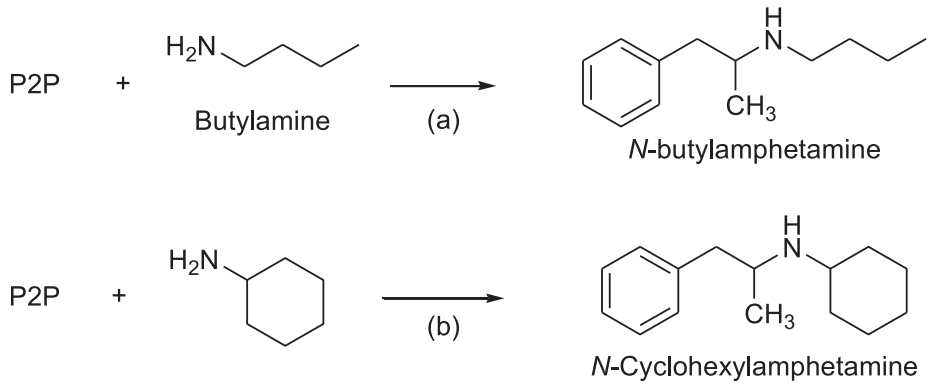

Fig. 8. Impurity profiles for NTS synthetic method. (a) *N*-Butylamphetamine synthetic route, (b) *N*-Clyclohexylamphetamine route.

adulterants during trafficking. While the pharmaceutical medicines demonstrate growing intelligence phenomena, tracking the specific legal drugs used in the MA production and the post-production modifications is an area of utmost interest.

Interestingly, in 2010, chlorpheniramine was identified in both Korea [31] and Iran [106], indicating a cross-border operation of the criminal networks. The emergence of these impurities was a direct indication of the use of legal medicines and their associated analgesic and co-ingredients containing ephedrine or pseudoephedrine.

Furthermore, Lee et al. [31] identified a pharmaceutical recipe based dimethyl sulfone from seized MA in Korea. The impurity was associated with the recipe used in medicinal drugs containing ephedrine/pseudoephedrine as well as an adulterant used in cutting MA. The impurity was previously identified in Korea (1996–2003) and USA (1996–2003) [30,107] emerged in Australia (1998–2002) [21], re-surfaced in (USA 2007) [108], Korea (2006–2011) [31] and Japan (2006–2007) [98]. The observed trend in the occurrence and re-emergence of dimethyl sulfone in the seized MA is potentially important in linking the operation of criminals in the countries. Although the determination of homogeneity might be very challenging, linking the dimethyl sulfone to its common source is essential for integrated intelligence.

Unlike other countries, a new profiling program based on pharmaceutical impurities conducted China recorded a new trend of impurity profiles of MA synthesized from ephedrine/pseudoephedrine [93]. Liu et al. reported tablets with Theophylline-Ephedrine, Ephedrine-Diphenhydramine, Pseudoephedrine, Dextromethorphan, and Chlorpheniramine as a new set of legal medicines commonly used as a source of ephedrine/pseudoephedrine. These drugs contain alkaline substances such as chlortrimeton, diphenhydramine, dextromethorphan, and triprolidine with the potential to form characteristic impurities. Their profiles information is not only used for monitoring the routine trends in precursor chemicals but also for the identification of the seized materials, smuggling patterns, and the determination of the synthetic routes [31,109].

Liu et al. systematically determined N^1,N^1, N^2-trimethyl-N^2-(1-phenylpropan-2-yl)ethane-1,2-diamine, which was assigned a characteristic impurity derived from pharmaceutical products containing ephedrine/pseudoephedrine and diphenhydramine. Unlike other pharmaceutical contaminants, the impurity is a product of a reaction between MA and traces of diphenhydramine derivative, which is co-extracted with ephedrine/pseudoephedrine. As a pharmaceutical co-extract of ephedrine/ephedrine derived diphenhydramine, the traces of the P2P precursor undergo band dissociation with HI in an I/P route to form 2-iodo-*N*, *N*-dimethylethanamine as an intermediate and traces of diphenyl methanol. The 2-iodo-*N*, *N*-dimethylethanamine then reacts with MA to form N^1, N^1, N^2-trimethyl-N^2-(1-phenylpropan-2-yl)ethane-1,2-diamine as shown in Fig. 9.

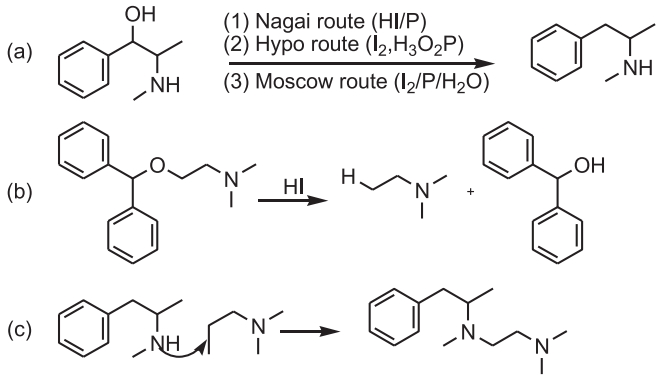

Fig. 9. A synthetic mechanism of N^1,N^1,N^2-trimethyl-N^2-(1-phenylpropaN-2-yl) ethane-1,2-diamine from diphenhydramine: (a) formation of methamphetamine, (b) dissociation of diphenhydramine to imine and diphenyl methanol, (c) reaction between imine and methamphetamine to form N^1,N^1,N^2-trimethyl-N^2-(1-phenylpropan-2-yl)ethane-1,2-diamine. Source [93].

In this reaction, the diphenhydramine is present as co-ingredients of legal medicine used for the synthesis of ephedrine/pseudoephedrine. The control of such drugs is essential for monitoring and identification of illicit production of ephedrine/pseudoephedrine from legal medicines.

1.3.3. Impurities discriminating ephedrine and pseudoephedrine synthetic routes

Ephedrine and pseudoephedrine are the basic precursors commonly used to synthesize MA beside the Phenyl-2-propanone [10,44,104,106]. A synthetic method using each of the precursor chemicals is associated with specific impurities that can intelligently discriminate against the MA synthetic method. From a forensic chemist's viewpoint, tracking the impurities down to the level of discrimination ephedrine and pseudoephedrine is an ultimate goal. Many MA profiling methods based on ephedrine/pseudoephedrine end up with non-discriminatory results, deriving their conclusions from an unresolved analytical process.

Precursor discrimination based on identified impurities is another interesting intelligence work. In a recent study by Dujourdy et al. [19], 43 target impurities in MA were successfully characterized and discriminated using chemometric methods.

Through clustering, the impurities identified from ephedrine, pseudoephedrine, and benzylmethylketone. In their work, 1-benzyl-3-methyl-naphthalene, and 1,3-dimethyl-2-phenyl-naphthalene were used to signify a route associated with ephedrine precursor.

Previously, *N*-formylmethamphetamine was considered a route-specific impurity for Leuckart route based MA [69,110]; however, the impurity has recently been identified in reductive amination based route for MA [20,99].

A realization of this challenge was reported by Khajeamiri et al. [106] in their work involving the reduction of ephedrine/pseudoephedrine with HI/red P. In their viewpoint, both ephedrine and pseudoephedrine react with HI/red P to form iodoephedrine, which undergoes a ring-opening to form commonly used route-specific impurities; the cis and *trans*-1,2-dimethyl-3-phenylaziridine [73].

Khajeamiri et al. articulated that 1,2-dimethyl-3-phenylaziridine is derivatized into *N*-methylmethamphetamine, *N*-ethylmethamphetamine, *N*-acetylmethamphetamine, acetic acid, *N*-benzyl-2-methylaziridine, methoxyphenyloxime amphetaminil, *d*-proline-1-phenylmethyl-methylester *N*-formylmethamphetamine, and dextromethorphane.

Reporting *N*-benzyl-2-methylaziridine as an emerging impurity, Khajeamiri et al. associated its formation with the conversion of 1,2-dimethyl-3-phenylaziridine into *N*-benzyl-2-methylaziridine during the formation of MA from ephedrine and pseudoephedrine.

Additionally, Khajeamiri et al. reported for the first time in 2012 the presence of Chlorpheniramine as a pharmaceutical-based impurity in MA. The impurity was later reported in Korea (2013) [31,49] and Iran [111]. The reports associated the impurity with pharmaceutical tablets used to synthesize pseudoephedrine precursors. Because chlorpheniramine is co-ingredient of pseudoephedrine tables only [49], it discriminates ephedrine and pseudoephedrine based MA.

1.3.4. Emerging signatures from stable isotopes

Stable isotopes composition in a MA sample has recently been used to profile MA seized in the USA [92] and Japan [112]. The technique employs natural abundance stable $\delta^{13}C$, $\delta^{12}C$, $\delta^{15}N$, $\delta^{14}N$, $\delta^{2}H$, $\delta^{1}H$ and, $\delta^{16}O$, $\delta^{17}O$, $\delta^{18}O$ and $\delta^{32}S$, $\delta^{33}S$, $\delta^{34}S$, $\delta^{36}S$ compositions in samples to establish chemical signatures for evaluating the links between MA seizures and their production batches [113–116]. The isotopes have specific natural rations; however, compartmental isotope ratios vary as per the geographical origin of the source [36] which is the basis for MA profiling based on stable isotopes.

The stable isotope ratio presented in delta values, δ in per mill where ("mil" = 1000), written ‰). The calculation of delta value as proposed by Barrie [117] is shown in the equation below.

$$\delta = 1000(R_{sample}\text{-}R_{standard})R_{standard} \quad [117]$$

Where R_{Sample} represents the ratio of the heavy to the light isotope measured for the sample while $R_{Standard}$ is the equivalent ratio for the standard.

Although the conventional analytical techniques through the existing GC [98], HPLC [110], GC-MS [33], and LC-MS-MS, ICP-MS [118–120], NMR [33,120] have been very effective in determining the type of precursor chemicals [100,121] synthetic route [16], and adulteration of illicit MA [28,48,54,122]; it has not been able to discriminate the precursors produced by different methods in the sense of identifying their origins. Furthermore, reductive amination routes usually have few impurity profiles that may not grant a successful impurity profiling [114]. The conventional techniques are also ineffective in traceability beyond sources of the starting materials [123].

In such circumstances, stable isotope analysis is a complementary technique that can individualize illicit MA samples based on the sources of their starting materials. Elsewhere, the method has successfully used in tracing studies in food [124,125], identification of illegal migrants [126], past human activities [122], and reconstruction of human diet [127].

In forensic intelligence of illicit drugs, stable isotopes technique unveil the hidden intrinsic precursor signatures that break the limits of the conventional impurity profiling by linking the seized MA and their batches to their synthetic origin [123]. Stable isotopes add value to the intelligence of illicit drugs based on impurity profiling.

MA produced by the same hidden laboratories, following the same method with the same kind of a precursor but different sources distinguished by examining their $\delta^{13}C$ and $\delta^{15}N$ values of their precursors [104]. In this respect, the variation of stable isotopes in seized MA can also trace the diversion of medicinal ephedrine for the illicit manufacture of MA.

Illicit ephedrine based MA was initially produced through a biosynthetic approach from the *ephedra* plant (Fig. 10(a)); however, a growing trend of total chemical synthesis (Fig. 10(b)) and semi-synthesis (Fig. 10(c)) have dominated the market.

The ephedrine produced through methods (a), (b) and (c) above will have different stable isotopic compositions used to track MA seizures. In principle, isotopic variation is due to different enrichment factors during the biochemical synthesis of raw materials for the precursor chemicals as well as the isotopic fractionation during the synthetic processes [60]. Although chemical synthesis a reliable source of ephedrine, the extraction from natural sources is another potential source for clandestine laboratories [104]. Therefore, an integrated approach with intelligence information collected beyond the starting materials is key to linking the operation of the criminal networks.

A complementary study on the use of stable isotopes techniques in evaluating the links between different MA seizures was reported by Iwata et al. [112] Benson et al. [36] and Billault et al. [123]. In a study by Billault et al., a variation of $\delta^{13}C$ and $\delta^{15}N$ was used to cluster seized MA and successfully established a link between different MA cases. The study successfully discriminated against semi-synthetic ephedrine from bio-synthetic or synthetic ephedrine by using $\delta^{13}C$. However; based on the fact the $\delta^{13}C$ values of acetaldehyde from sugar are more optimistic compared to C_3-photosynthetic plants or products derived from petroleum, it could not differentiate biosynthetic ephedrine from synthetic ephedrine.

Recently, a stable isotopes technique was used to investigate the unique profiles of stable nitrogen isotopic composition in seized MA samples [128]. In this work, the stable isotopes variation can be due to the isotopic variations in the starting materials, isotopic fractionation during the synthetic processes, and due to analytical errors. It is therefore essential to draw a conclusion based on the magnitude of the variation to eliminate the influence of isotopic fractionation and analytical errors. A variation of 0.9‰ $\delta^{15}N$ evidenced a difference in batches of production and subsequently, different ephedrine sources used as starting materials for the production of MA. Iwata et al. [128] further used the stable isotope technique to classify the MA seizures based on their synthetic batches. Based on the criteria proposed by Iwata et al. [128], $\Delta\delta < 0.4$‰ represents a significant variation in batches.

Interestingly, stable isotope technology is making an in-road towards the discrimination of illicit synthetic/semi-synthetic illegal drugs based on their synthetic routes and their associated reactions conditions beyond its conventional use in discriminating the sources for MA. As a growing profiling method, it complements the impurity profiling by linking the synthetic routes to isotopes ratios.

Billault et al. reported startling scientific research that seems to

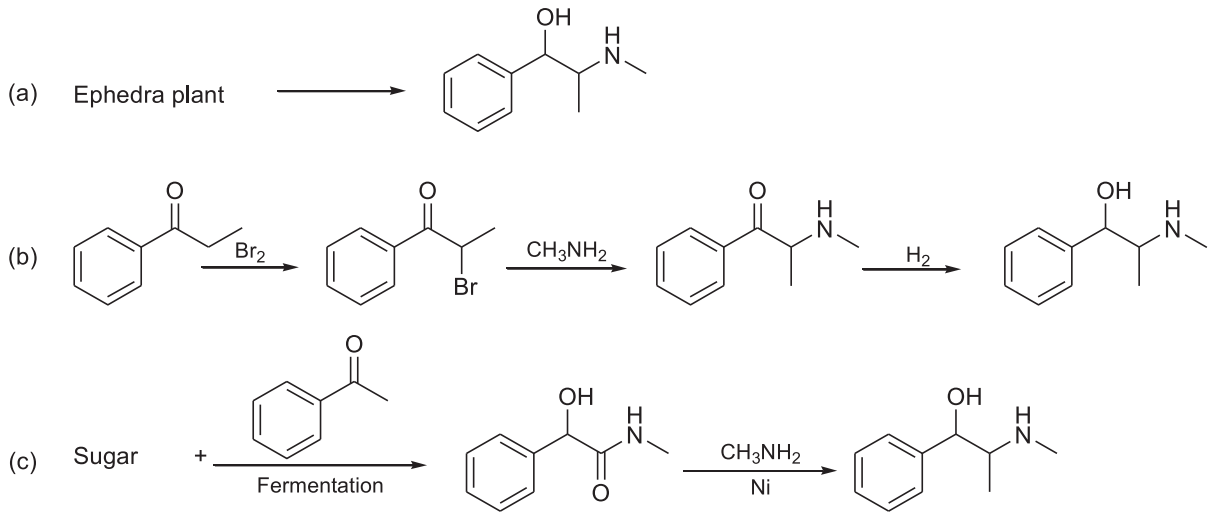

Fig. 10. Different sources of ephedrine: (a) extraction from ephedra plant, (b) chemosynthesis, (c) semi-synthesis.

confirm the use of stable isotopes in linking MA batches to their respective synthetic routes. These results were the first to be reported in linking the $\delta^{13}C$ values of the precursors in distinguishing synthetic routes of seized MA and their derivatives. Having investigated the relationship between $\delta^{13}C$ and $\delta^{15}N$ of the precursors and those of 45 samples of MDMA, the authors demonstrated how the number of synthesis steps influenced the value of $\delta^{13}C$ in the seized MA samples and consequently discriminated the synthetic routes possessing more than one step.

Similarly, the discrimination of synthetic routes using stable isotopes is established by comparing the $\delta^{15}N$ values of the origin precursors and the seized MA. The values of $\delta^{15}N$ in MA are dependent on the source of nitrogen used, the route by which the MDMA is synthesized [114,115], and the experimental conditions employed [116,123,129].

Previous work by Billault et al. discriminated MA based on their synthetic origins, synthetic routes as well a close variation of the stable isotopes based reaction conditions of MA tested.

2. Conclusion

In this review, we have discussed the impurities and stable isotopes signatures found in illicit MA. The signatures are critical in the intelligence of illegal drugs, linking the illegal drugs with their sources, synthetic methods, synthetic batches, and their geographical origin. Although stable isotopes have been influential in discriminating seizures based on their origin, it is evident from this review that its potential in profiling MA has not been fully explored.

The review highlights further how the integration of impurity profiling with stable isotopes signatures coupled with chemometric techniques complements the existing intelligence gaps. The review illustrates how an assortment of legally available chemicals and medicines used to mask the controlled substances. It has also been shown in this review how precursor chemicals come with their corresponding stable isotopes and tracking them down to their stable isotopes has been essential in discriminating the seizures based on their original starting materials resulting in comprehensive profiling.

Studies linking stable isotope technique in profiling MA are undoubtedly limited, perhaps because of the advanced instrumentations. In furtherance of monitoring the dynamics of the MA, drug markets, and the advances of the criminal networks, future research is indispensable. Future research should focus on the diversity of both licit and illicit starting materials, complementing impurity profiling with stable isotopes, building knowledge with regards to the newly identified MA profiles, and finally; coupling the methods with chemometric techniques.

CRediT authorship contribution statement

Isaac Onoka: Conceptualization, Writing - original draft. **Andrew Toyi Banyika:** Writing - review & editing. **Protibha Nath Banerjee:** Supervision. **John J. Makangara:** Supervision, Writing - review & editing. **Laurence Dujourdy:** Resources, Writing - review & editing.

Declaration of competing interest

The authors declare that there is no conflict of interest.

Acknowledgment

Thanks to the University of Dodoma, Tanzania for allowing the ongoing study on the profiling of methamphetamine. We would also like to thank Dr. Mellony Manning for proofreading and checking the language.

References

[1] UN, United Nations treaty collection: United Nations convention against illicit traffic in narcotic drugs and psychotropic substances 1–37 (1988).
[2] INCB, International Narcotics Control Board: List of Precursors and Chemicals Frequently Used in the Illicit Manufacture of Narcotic Drugs and Psychotropic Substances under International Control, sixth ed., Vienna International Centre, Vienna, 2018.
[3] UNODC, World Drug Report, vol. 156, United Nations Office on Drugs and Crime, 2016.
[4] DEA, "Drug Enforcement Administration, Methamphetamine," Divers, Control Div, Drug Chem. Eval. Sect. (2020) 4250.
[5] UNODC, World Drug Report, United Nations Office on Drugs and Crime, Vienna, 2019.
[6] B.A. Perillo, R.F.X. Klein, E.S. Franzosa, Recent advances by the U.S. Drug Enforcement Administration in drug signature and comparative analysis, Forensic Sci. Int. 69 (1) (1994), 1–6.
[7] UNODC, in: United Nations Office on Drugs and Crime,"The Challenge of Synthetic Drugs in East and South-East Asia and Oceania Trends and Patterns of Amphetamine-type Stimulants and New Psychoactive Substances, vol. 35, 2015.

[8] UNODC, World Drug Report,United Nations Office on Drugs and Crime: Market Analysis of Plant-Based Drugs, 2017.
[9] UNODC, World Drug Report,United Nations Office on Drugs and Crime: Global Overview of Drug Demand and Supply, 2017.
[10] J.C. Maxwell, M.L. Brecht, " Methamphetamine, Here we go again? Addict. Behav. 36 (12) (Dec. 2011) 1168–1173.
[11] K. Tanaka, T. Ohmori, Y. Togawa, S. Seta, Impurity profiling analysis of methamphetamine seized in Japan, Forensic Sci. Int. 69 (1994) 97–102.
[12] T.K. Hiroyuki Inoue, Tatsuyuki Kanamori, Yuko T. Iwata, Yoshihito Ohmae, Kenji Tsujikawa, Shuji Saitoh, Methamphetamine impurity profiling using a 0.32 mm i.d. nonpolar capillary column, Forensic Sci. Int. 135 (1) (2003) 42–47.
[13] J.K. Cunningham, R.C. Callaghan, D. Tong, L.M. Liu, H.Y. Li, W.J. Lattyak, Changing over-the-counter ephedrine and pseudoephedrine products to prescription only: impacts on methamphetamine clandestine laboratory seizures, Drug Alcohol Depend. 126 (1–2) (2012) 55–64.
[14] J.K. Cunningham, I. Bojorquez, O. Campollo, L.M. Liu, J.C. Maxwell, "Mexico's methamphetamine precursor chemical interventions: impacts on drug treatment admissions, Addiction 105 (11) (1983) 1973, 2010.
[15] C.V. Owens, Remediation of manufactured methamphetamine in clandestine laboratories. A literature review, J. Chem. Health Saf. 24 (5) (2017) 23–37.
[16] R.J.H. Waddell-Smith, A review of recent advances in impurity profiling of illicit MDMA samples, J. Forensic Sci. 52 (6) (2007) 1297–1304.
[17] K. Tsujikawa, et al., Profiling of seized methamphetamine putatively synthesized by reductive amination of 1-phenyl-2-propanone, Forensic Toxicol. 30 (1) (Jan. 2012) 70–75.
[18] F. Palhol, S. Boyer, N. Naulet, M. Chabrillat, Impurity profiling of seized MDMA tablets by capillary gas chromatography, Anal. Bioanal. Chem. 374 (2) (2002) 274–281.
[19] L. Dujourdy, et al., Drug intelligence based on organic impurities in illicit MA samples, Forensic Sci. Int. 177 (2–3) (2008) 153–161.
[20] Y. Qi, I. Evans, A. Mccluskey, "New impurity profiles of recent Australian imported ' ice ': methamphetamine impurity profiling and the identification of (pseudo) ephedrine and Leuckart specific marker compounds 169 (2007) 173–180.
[21] Y. Qi, I.D. Evans, A. McCluskey, "Australian Federal Police seizures of illicit crystalline methamphetamine ('ice') 1998-2002: impurity analysis, Forensic Sci. Int. 164 (2–3) (2006) 201–210.
[22] K. Kuwayama et al., "Comparison and classification of methamphetamine seized in Japan and Thailand using gas chromatography with liquid-liquid extraction and solid-phase microextraction," Forensic Sci. Int., vol. 175, no. 2–3, pp. 85–92, Mar. 2008.
[23] V. Puthaviriyakorn, N. Siriviriyasomboon, J. Phorachata, W. Pan-ox, T. Sasaki, K. Tanaka, Identification of impurities and statistical classification of methamphetamine tablets (Ya-Ba) seized in Thailand, Forensic Sci. Int. 126 (2) (2002), 105–113.
[24] J.X. Zhang, D.M. Zhang, X.G. Han, Identification of impurities and statistical classification of methamphetamine hydrochloride drugs seized in China, Forensic Sci. Int. 182 (1–3) (2008) 13–19.
[25] F.M. Dayrit, M.C. Dumlao, Impurity profiling of methamphetamine hydrochloride drugs seized in the Philippines, Forensic Sci. Int. 144 (1) (2004) 29–36.
[26] Y.T. Iwata, K. Kuwayama, K. Tsujikawa, H. Miyaguchi, T. Kanamori, H. Inoue, Seized methamphetamine samples with unique profiles of stable nitrogen isotopic composition documented by stable isotope ratio mass spectrometry, Forensic Toxicol. 28 (2) (2010) 119–123.
[27] Y. Makino, Simple HPLC method for detection of trace ephedrine and pseudoephedrine in high-purity methamphetamine, Biomed. Chromatogr. 26 (3) (2012) 327–330.
[28] J.C. Maxwell, "A new survey of methamphetamine users in treatment: who they are, why they like 'meth,' and why they need additional services, Subst. Use Misuse 49 (6) (2014) 639–644.
[29] P. Vazquez-Roig, B. Kasprzyk-Hordern, C. Blasco, Y. Pico, Stereoisomeric profiling of drugs of abuse and pharmaceuticals in wastewaters of Valencia (Spain), Sci. Total Environ. 494 (495) (2014) 49–57.
[30] J.H.P. Jae Sin Lee, Wun Kyung Yang, Eun young han, soo yeun lee, yong hoon park, Mi Ae lim, hee sun chung, "monitoring precursor chemicals of methamphetamine through enantiomer profiling, Forensic Sci. Int. 173 (1) (2007) 68–72.
[31] S. Choe, S. Heo, H. Choi, E. Kim, H. Chung, J. Lee, Analysis of pharmaceutical impurities in the methamphetamine crystals seized for drug trafficking in Korea, Forensic Sci. Int. 227 (1–3) (Apr. 2013) 48–51.
[32] A.L. Pikkarainen, Systematic approach to the profiling analysis of illicit amphetamine, Forensic Sci. Int. 82 (2) (1996) 141–152.
[33] J.M. Płotka, C. Morrison, D. Adam, M. Biziuk, Chiral analysis of chloro intermediates of methylamphetamine by one-dimensional and multidimentional NMR and GC/MS, Anal. Chem. 84 (13) (Jul. 2012) 5625–5632.
[34] C.S.L. Jonson, Amphetamine profiling-improvements of data processing, Forensic Sci. Int. 69 (1994) 45–54.
[35] R.K. Shukla, J.L. Crump, E.S. Chrisco, An evolving problem: methamphetamine production and trafficking in the United States, Int. J. Drug Pol. 23 (6) (2012) 426–435.
[36] S. Benson, C. Lennard, P. Maynard, C. Roux, Forensic applications of isotope ratio mass spectrometry - a review, Forensic Sci. Int. 157 (1) (2006) 1–22.
[37] B.J. Ko, S.I. Suh, Y.J. Suh, M.K. In, S.H. Kim, J.H. Kim, (1S,2S)-1-Methylamino-1-phenyl-2-chloropropane: route specific marker impurity of methamphetamine synthesized from ephedrine via chloroephedrine, Forensic Sci. Int. 221 (1–3) (Sep. 2012) 92–97.
[38] M. Collins, H. Salouros, A review of some recent studies on the stable isotope profiling of methylamphetamine: is it a useful adjunct to conventional chemical profiling? Sci. Justice 55 (1) (2015) 2–9.
[39] H. Segawa, et al., Enantioseparation of methamphetamine by supercritical fluid chromatography with cellulose-based packed column, Forensic Sci. Int. 273 (Apr. 2017) 39–44.
[40] K. Tsujikawa, K. Kuwayama, H. Miyaguchi, T. Kanamori, Y.T. Iwata, H. Inoue, Chemical profiling of seized methamphetamine putatively synthesized from phenylacetic acid derivatives, Forensic Sci. Int. 227 (1–3) (Apr. 2013) 42–44.
[41] United Nations Office on Drugs and Crime, A Practical Guide to Methamphetamine Characterization/Impurity Profiling : Method Procedures , Mass Spectral Data of Selected Impurities , and Literature References, 2000. August.
[42] G. Man, B. Stoeber, K. Walus, An assessment of sensing technologies for the detection of clandestine methamphetamine drug laboratories, Forensic Sci. Int. 189 (1–3) (2009) 1–13.
[43] United Nations Office on Drugs and Crime, Drug Characterization/impurity Profiling , Background and Concepts Manual for Use by National Law Enforcement Authorities and Drug Testing Laboratories, 2001.
[44] P.M. Marie Morelato, Simon Baechler, Olivier Ribaux, Alison Beavis, Mark Tahtouh, Paul Kirkbride, Claude Roux, "Forensic intelligence framework-Part I: induction of a transversal model by comparing illicit drugs and false identity documents monitoring, Forensic Sci. Int. 236 (2014) 181–190.
[45] N. NicDaéid, S. Jayaram, W.J. Kerr, Elemental profiling using ICPMS of methylamphetamine hydrochloride prepared from proprietary medication using the Moscow and hypophosphorous synthesis, Sci. Justice 53 (3) (2013) 278–285.
[46] N. Stojanovska, S. Fu, M. Tahtouh, T. Kelly, A. Beavis, K.P. Kirkbride, A review of impurity profiling and synthetic route of manufacture of methylamphetamine, 3,4-methylenedioxymethylamphetamine, amphetamine, dimethylamphetamine and p-methoxyamphetamine, Forensic Sci. Int. 224 (1–3) (10-Jan-2013). . pp. 8–26.
[47] Y.O. Kyoko Uekusa, Makiko Hayashida, Nobuyuki Saito, Kunihiro Mashiko, Kenji Hara, Brian Waters, Methamphetamine and amphetamine concentrations in survivors of body-packer syndrome in Japan, Forensic Sci. Int. 227 (1–3) (2013) 45–47.
[48] V. Kunalan, N.N. Daéid, W.J. Kerr, H.A.S. Buchanan, A.R. McPherson, Characterization of route specific impurities found in methamphetamine synthesized by the Leuckart and reductive amination methods, Anal. Chem. 81 (17) (Sep. 2009) 7342–7348.
[49] J.P. Jaesin Lee, Yonghoon Park, Wonkyung Yang, Heesun chung, wonjun choi, hiroyuki inoue, kenji kuwayama, "cross-examination of liquid-liquid extraction (LLE) and solid-phase microextraction (SPME) methods for impurity profiling of methamphetamine, Forensic Sci. Int. 215 (1–3) (2012) 175–178.
[50] Y. Makino, "Simple HPLC method for detection of trace ephedrine and pseudoephedrine in high-purity methamphetamine," Biomed. Chromatogr., vol. 26, no. 3, pp. 327–330, Mar. 2012.
[51] H.I. Toshiyasu Mikuma, Yuko T. Iwata, Hajime Miyaguchi, Kenji Kuwayama, Kenji Tsujikawa, Tatsuyuki Kanamori, ", The use of a sulfonated capillary on chiral capillary electrophoresis/mass spectrometry of amphetamine-type stimulants for methamphetamine impurity profiling, Forensic Sci. Int. 249 (2015) 59–65.
[52] C. Zingg, "The Analysis of Ecstasy Tablets in a Forensic Drug Intelligence Perspective," Doctoral Dissertation, Université de Lausanne, Faculté de droit et des sciences criminelles, 2005.
[53] J. Broséus, N. Gentile, F. Bonadio Pont, J.M. Garcia Gongora, L. Gasté, P. Esseiva, Qualitative, quantitative and temporal study of cutting agents for cocaine and heroin over 9 years, Forensic Sci. Int. 257 (2015) 307–313.
[54] N. Stojanovska, S. Fu, M. Tahtouh, T. Kelly, A. Beavis, K.P. Kirkbride, A review of impurity profiling and synthetic route of manufacture of methylamphetamine, 3,4-methylenedioxymethylamphetamine, amphetamine, dimethylamphetamine and p-methoxyamphetamine, Forensic Sci. Int. 224 (1–3) (2013) 8–26.
[55] S.A.S. Kimberly C Brouwer, Patricia Case, Rebeca Ramos, Carlos Magis-Rodriguez, Jesus Bucardo, Thomas L. Patterson, "Trends in production, trafficking, and consumption of methamphetamine and cocaine in Mexico," Subst, Use Misuse 41 (5) (2006) 707–727.
[56] D.I. Wan Nur, Syuhaila Mat Desa, "Impurity profiling of amphetamine and methamphetamine using gas chromatography mass spectrometry (GCMS) Harmonised Methods, Sains Malays. 46 (1) (2017) 149–156.
[57] J.K. Cunningham, J.C. Maxwell, O. Campollo, L.M. Liu, W.J. Lattyak, R.C. Callaghan, "Mexico's precursor chemical controls: emergence of less potent types of methamphetamine in the United States, Drug Alcohol Depend. 129 (1–2) (2013) 125–136.
[58] M. Morelato, A. Beavis, M. Tahtouh, O. Ribaux, K.P. Kirkbride, C. Roux, The use of methylamphetamine chemical profiling in an intelligence-led perspective and the observation of inhomogeneity within seizures, Forensic Sci. Int. 246 (Jan. 2015) 55–64.
[59] H. Salouros, M. Collins, A.V. George, S. Davies, Isolation and identification of three by-products found in methylamphetamine synthesized by the Emde

route, J. Forensic Sci. 55 (3) (2010) 605–615.
[60] M. Morelato, A. Beavis, M. Tahtouh, O. Ribaux, K.P. Kirkbride, C. Roux, The use of methylamphetamine chemical profiling in an intelligence-led perspective and the observation of inhomogeneity within seizures, Forensic Sci. Int. 246 (2015) 55–64.
[61] B.J. Ko, S.I. Suh, Y.J. Suh, M.K. In, S.H. Kim, The impurity characteristics of methamphetamine synthesized by Emde and Nagai method, Forensic Sci. Int. 170 (2–3) (Aug. 2007) 142–147.
[62] H. Inoue, Y.T. Iwata, K. Kuwayama, Characterization and profiling of methamphetamine seizures, J. Health Sci. 54 (6) (2008) 615–622.
[63] J.H.P. Jae Sin Lee, Wun Kyung Yang, Eun young han, soo Yeun lee, yong hoon park, Mi Ae lim, hee sun chung, "analysis of the impurities in the methamphetamine synthesized by three different methods from ephedrine and pseudoephedrine, Forensic Sci. Int. 161 (2–3) (Sep. 2006) 209–215.
[64] B.J. Ko, S.I. Suh, Y.J. Suh, M.K. In, S.H. Kim, J.H. Kim, (1S,2S)-1-Methylamino-1-phenyl-2-chloropropane: route specific marker impurity of methamphetamine synthesized from ephedrine via chloroephedrine, Forensic Sci. Int. 221 (1–3) (2012) 92–97.
[65] A.C. Allen, M.L. Stevenson, S.M. Nakamura, R.A. Ely, Differentiation of illicit phenyl-2-propanone synthesized from phenylacetic acid with acetic anhydride versus lead (II) acetate, J. Forensic Sci. 37 (1) (1992) 13235J.
[66] J.R.V. Person, C. Eric, Jennifer A. Meyer, Structural determination of the principal byproduct of the lithium-ammonia reduction method of methamphetamine manufacture, J. Forensic Sci. 50 (1) (2005). JFS2004204-J2004209.
[67] D.C.M. Ely, A. Roger, Lithium-ammonia reduction of ephedrine to methamphetamine: an unusual clandestine synthesis, J. Forensic Sci. 35 (3) (1990) 720–723.
[68] A.M.A. Verweij, Impurities in illicit drug preparations: amphetamine and methamphetamine, Forensic Sci. Rev. 1 (1) (1989) 1–11.
[69] T.C.K. Robert P Barron, Alice V. Kruegel, James M. Moore, Identification of impurities in illicit methamphetamine samples, J. Assoc. Off. Anal. Chem. 57 (5) (1974) 1147–1158.
[70] A.V.K. Kram, T. C, The identification of impurities in illicit methamphetamine exhibits by gas chromatography/mass spectrometry and nuclear magnetic resonance spectroscopy, J. Forensic Sci. 22 (1) (1977) 40–52.
[71] K.L. Windahl, M.J. McTigue, J.R. Pearson, S.J. Pratt, J.E. Rowe, E.M. Sear, Investigation of the impurities found in methamphetamine synthesised from pseudoephedrine by reduction with hydriodic acid and red phosphorus, Forensic Sci. Int. 76 (2) (1995) 97–114.
[72] T.S. Cantrell, B. John, L. Johnson, A.C. Allen, A study of impurities found in methamphetamine synthesized from ephedrine, Forensic Sci. Int. 39 (1) (1988) 39–53.
[73] H.F. Skinner, Methamphetamine synthesis via hydriodic acid/red phosphorus reduction of ephedrine, Forensic Sci. Int. 48 (2) (1990) 123–134.
[74] N. Stojanovska, S. Fu, M. Tahtouh, T. Kelly, A. Beavis, K.P. Kirkbride, A review of impurity profiling and synthetic route of manufacture of methylamphetamine, 3,4-methylenedioxymethylamphetamine, amphetamine, dimethylamphetamine and p-methoxyamphetamine, Forensic Sci. Int. 224 (1–3) (2013) 8–26.
[75] V. Lekskulchai, K. Carter, A. Poklis, W. Soine, "GC-MS analysis of methamphetamine impurities :reactivity of (+)-or (-)-Chloroephedrine and cis- or trans- 1,2- dimethyl-3-phenylazi ridine 24, October, 2000, pp. 602–605.
[76] K.W. Allen A, Methamphetamine from ephedrine: I. Chloroephedrines and aziridines, J. Forensic Sci. 32 (4) (1986) 953–962.
[77] W.D. Barker, U. Antia, A study of the use of Ephedra in the manufacture of methamphetamine, Forensic Sci. Int. 166 (2–3) (2007) 102–109.
[78] B.J. Ko, S.I. Suh, Y.J. Suh, M.K. In, S.H. Kim, The impurity characteristics of methamphetamine synthesized by Emde and Nagai method, Forensic Sci. Int. 170 (2–3) (2007) 142–147.
[79] D. Albouy, G. Etemad-Moghadam, M. Vinatoru, M. Koenig, "Regenerative role of the red phosphorus in the couple 'HIaq/Pred, J. Organomet. Chem. 529 (1–2) (1997) 295–299.
[80] V. Kunalan, W.J. Kerr, N. NicDaéid, Clarification of route specific impurities found in methylamphetamine synthesised using the Birch method, Forensic Sci. Int. 223 (1–3) (2012) 321–329.
[81] J. L. J. Fracia S. Martinez, Daniel M. Roesch, "Isolation of methamphetamine from 1-(1',4'-Cyclohexadienyl)-2-methylaminopropane 46 (CMP) using potassium permanganate," microgram repr. With permis. From J. Clandestine Lab. Investig. Chem. Assoc., 46AD.
[82] S.G. Toske, J.L. Brown, E.E. Miller, M.Z. Phillips, S.C. Kerr, P.A. Hays, Recent methamphetamine profiling trends: tracking the nitrostyrene method used for P2P production, Forensic Chem. 13 (2019) 100140. October 2018.
[83] A.M. Zaputrayaev, B. A, O.Y. Velitskaya, L.S. Glikina, Khaletskii, Improvement of methylbenzyl ketone synthesis, Meditsinskaya Promyshlennost SSSR 14 (1) (1960) 48–51.
[84] G.D. Julian, P. L, J.J. Oliver, R.H. Kimball, A.B. Pike, Jefferson, Methyl benzyl ketone from a-phenylacetoacetonitril, Org. Synth. 18 (1948) 54–55.
[85] I. Murahashi, S., Haniwara, N., and Hirao, "Phenylacetone," 3616, 1950.
[86] W.F. Bruce, "Cholestanone," Org. Synth. II (1943) 139–140.
[87] J.W.I. Wilson, Synthesis of d,l-amphetamine sulfate labeled with 14C, J. Am. Pharmaceut. Assoc. 39 (1950) 687–688.
[88] H.R. Sund, E. H, Henze, Alkyl benzyl ketones and hydantoin derivatives, J. Chem. Eng. Data 15 (1) (1970) 200–201.
[89] K. Okabe, T. Ohwada, T. Ohta, Shudo, Novel electrophilic species equivalent to a-keto cations: reactions of O,O-diprotonated nitro olefins with benzenes yield arylmethyl ketones, J. Org. Chem. 54 (4) (1989) 733–734.
[90] R.H.H.B. Hass, A. G, Susie, "nitro alkene derivative, J. Org. Chem. 53 (9) (1950) 8–14.
[91] M. Collins, "Illicit drug profiling: the Australian experience–revisited, Aust. J. Forensic Sci. 49 (6) (Nov. 2017) 591–604.
[92] S.G. Toske, D.R. Morello, J.M. Berger, E.R. Vazquez, The use of δ13C isotope ratio mass spectrometry for methamphetamine profiling: comparison of ephedrine and pseudoephedrine-based samples to P2P-based samples, Forensic Sci. Int. 234 (1) (Jan. 2014) 1–6.
[93] C. Liu, W. Jia, Y. Han, Z. Hua, The structure identification of a diphenhydramine-related impurity in methamphetamine, Drug Test. Anal. 10 (7) (2018) 1192–1197.
[94] M. Morelato, A. Beavis, M. Tahtouh, O. Ribaux, P. Kirkbride, C. Roux, "The use of forensic case data in intelligence-led policing : the example of drug profiling, Forensic Sci. Int. 226 (1–3) (2013) 1–9.
[95] L.E. Wilson, M.E. Gahan, C. Lennard, J. Robertson, Developing a strategic forensic science risk management system as a component of the forensic science system of systems, Aust. J. Forensic Sci. 52 (2018) 208–221, https://doi.org/10.1080/00450618.2018.1510032.
[96] H. Salouros, Illicit drug chemical profiling: current and future state, Aust. J. Forensic Sci. 50 (6) (Nov. 2018) 689–696.
[97] A. Reza, M. Faizi, F. Sohani, T. Baheri, F. Kobarfard, Determination of impurities in illicit methamphetamine samples seized in Iran, Forensic Sci. Int. 217 (1–3) (2012) 204–206.
[98] H. Inoue, K. Kuwayama, Y.T. Iwata, T. Kanamori, K. Tsujikawa, H. Miyaguchi, Simple and simultaneous detection of methamphetamine and dimethyl sulfone in crystalline methamphetamine seizures by fast gas chromatography, Forensic Toxicol. 26 (1) (2008) 19–22.
[99] V. Kunalan, N.N. Daéid, W.J. Kerr, H.A.S. Buchanan, A.R. McPherson, Characterization of route specific impurities found in methamphetamine synthesized by the Leuckart and reductive amination methods, Anal. Chem. 81 (17) (2009) 7342–7348.
[100] T.S.C. Allen Andrew, Synthetic reductions in clandestine amphetamine and methamphetamine laboratories: a review, Forensic Sci. Int. 42 (3) (1989) 183–199.
[101] W.F. Maier, S.J. Chettle, R.S. Rai, G. Thomas, Metamorphosis of palladium and its relation to selectivity in the Rosenmund reaction, J. Am. Chem. Soc. 108 (10) (May 2002) 2608–2616.
[102] S.G.T. Jennifer, B. McConnell, Jaclyn L. Brown, Jennifer M. Tuten, Erin E. Miller, Monica Z. Phillips, Etienne R. Vazquez, Ira S. Lurie, Patrick A. Haysa, Elizabeth M. Guesta, Isolation and characterization of a newly identified impurity in methamphetamine synthesized via reductive amination of 1-phenyl-2-propanone (P2P) made from phenylacetic acid/lead (II) acetate, Drug Test. Anal. 9 (3) (2017) 453–461.
[103] R.W. Hay, M.A. Bond, Kinetics of the decarboxylation of acetoacetic acid, Aust. J. Chem. 20 (9) (1967) 1823–1828.
[104] N. Kurashima, Y. Makino, S. Sekita, Y. Urano, T. Nagano, Determination of origin of ephedrine used as precursor for illicit methamphetamine by carbon and nitrogen stable isotope ratio analysis, Anal. Chem. 76 (14) (2004) 4233–4236.
[105] K. L, P.E. Northrop Dm, Methamphetamine manufacture from cold and allergy medications containing pseudoephedrine in multi-ingredient liquid and softgel preparations, J. Clandestine Lab. Investig. Chem. Assoc. 15 (2) (2005) 11–19.
[106] A.R. Khajeamiri, M. Faizi, F. Sohani, T. Baheri, F. Kobarfard, Determination of impurities in illicit methamphetamine samples seized in Iran, Forensic Sci. Int. 217 (1–3) (Apr. 2012) 204–206.
[107] Drug Enforcement Administration Office of Forensic Sciences, "Methamphetamine "'ice"' with dimethyl sulfone in Hawai, Micro 29 (1996) 196–197.
[108] Drug Enforcement Administration Office of Forensic Sciences, "'Ice" methamphetamine concealed in a (presumed child's) mini-purse/keychain in New York city, Microgram Bull 40 (88) (2007).
[109] S.H. DiPari Sc, J.A. Bordelon, Desloratadine: the reaction byproduct of the reduction of cold tablets containing loratadine with hydriodic acid/red phosphorus, Micro J. 3 (1–2) (2005) 69–77.
[110] I.S. Lurie, C.G. Bailey, D.S. Anex, M.J. Bethea, T.D. McKibben, J.F. Casale, Profiling of impurities in illicit methamphetamine by high-performance liquid chromatography and capillary electrochromatography, J. Chromatogr. A 870 (1–2) (2000) 53–68.
[111] A. Shekari, M. Akhgari, F. Jokar, Z. Mousavi, Impurity characteristics of street methamphetamine crystals seized in Tehran, Iran, J. Subst. Use 21 (5) (Sep. 2016) 501–505.
[112] H.M. Yuko, T. Iwata, Kenji Kuwayama, Kenji Tsujikawa, T. K, H. Inoue, Evaluation method for linking methamphetamine seizures using stable carbon and nitrogen isotopic compositions: a complementary study with impurity profiling, Rapid Commun. Mass Spectrom. 22 (2008) 3816–3822.
[113] A.T.W. Dunbar John, Determination of geographic origin of caffeine by stable isotope analysis, Anal. Chem. 54 (3) (1982) 590–592.
[114] F. Mas, B. Beemsterboera, A.C. Veltkamp, A.M.A. Verweij, "Determination of ' common-batch ' members in a methylamphetamine samples by measuring the natural isotope abundances : a preliminary study, Forensic Sci. Int. 71 (1995) 225–231.
[115] J.F. Carter, E.L. Titterton, M. Murray, R. Sleeman, Isotopic characterisation of 3,4-methylenedioxyamphetamine and 3,4-

methylenedioxymethylamphetamine (ecstasy), Analyst 127 (6) (2002) 830–833.
[116] F. Palhol, C. Lamoureux, N. Naulet, 15N isotopic analyses: a powerful tool to establish links between seized 3,4-methylenedioxymethamphetamine (MDMA) tablets, Anal. Bioanal. Chem. 376 (4) (2003) 486–490.
[117] A. Barrie, Automated analysis of light-element stable isotopes by isotope ratio mass spectrometry, Mass Spectrom. Soils (1996). ID (NAID) 10017430001.
[118] R. Nageswara Rao, M.V.N. Kumar Talluri, An overview of recent applications of inductively coupled plasma-mass spectrometry (ICP-MS) in determination of inorganic impurities in drugs and pharmaceuticals, J. Pharmaceut. Biomed. Anal. 43 (1) (2007) 1–13.
[119] M. Y, I. T, S. S, Analysis of inorganic impurities in seized methamphetamine samples, Forensic Sci. Int. 69 (1) (1994) 89–95.
[120] P.A. Hays, Proton nuclear magnetic resonance spectroscopy (NMR) methods for determining the purity of reference drug standards and illicit forensic drug seizures, J. Forensic Sci. 50 (6) (2005) 1–19.
[121] K.A. Moore, A.H. Lichtman, A. Poklis, J.F. Borzelleca, α-Benzyl-N-methylphenethylamine (BNMPA), an impurity of illicit methamphetamine synthesis: pharmacological evaluation and interaction with methamphetamine, Drug Alcohol Depend. 39 (2) (1995) 83–89.
[122] B. Chase, D. Meiggs, P. Ajithprasad, P.A. Slater, What is left behind: advancing interpretation of pastoral land-use in Harappan Gujarat using herbivore dung to examine biosphere strontium isotope (87 Sr/86 Sr) variation, J. Archaeol. Sci. 92 (2018) 1–12.
[123] I. Billault, F. Courant, L. Pasquereau, S. Derrien, R.J. Robins, N. Naulet, Correlation between the synthetic origin of methamphetamine samples and their 15N and 13C stable isotope ratios, Anal. Chim. Acta 593 (1) (2007) 20–29.
[124] A. Rossmann, Determination of stable isotope ratios in food analysis, Food Rev. Int. 17 (3) (2001) 347–381.
[125] R. Pillonel, R. Badertscher, P. Froidevaux, G. Haberhauer, S. Hölzl, P. Horn, A. Jakob, E. Pfammatter, U. Piantini, A. Rossmann, Tabacchi, Stable isotope ratios, major, trace and radioactive elements in emmental cheeses of different origins, LWT - Food Sci. Technol. (Lebensmittel-Wissenschaft -Technol.) 36 (6) (2003) 615–623.
[126] H. Shaw, J. Montgomery, R. Redfern, R. Gowland, J. Evans, Identifying migrants in Roman London using lead and strontium stable isotopes, J. Archaeol. Sci. 66 (2016) 57–68.
[127] C. Rissech, A. Pujol, N. Christie, L. Lloveras, M.P. Richards, B.T. Fuller, Isotopic reconstruction of human diet at the Roman site (1st-4th c. AD) of Carrer Ample 1, Barcelona, Spain, J. Archaeol. Sci. Reports 9 (2016) 366–374.
[128] Y.T. Iwata, K. Kuwayama, K. Tsujikawa, H. Miyaguchi, T. Kanamori, H. Inoue, Seized methamphetamine samples with unique profiles of stable nitrogen isotopic composition documented by stable isotope ratio mass spectrometry, Forensic Toxicol. 28 (2) (Jul. 2010) 119–123.
[129] F. Palhol, C. Lamoureux, M. Chabrillat, N. Naulet, 15N/14N isotopic ratio and statistical analysis: an efficient way of linking seized Ecstasy tablets, Anal. Chim. Acta 510 (1) (2004) 1–8.