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A review on Chemistry and Analytical challenges of Methamphetamine

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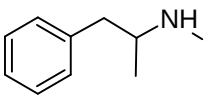
Abstract

Analytical chemistry not only helps to control drug abuse through identification, but it also helps in the field of sports by detecting drug traces in athletes. Methamphetamine is one such drug that has been widely used by athletes, and its detection in the blood has been a real challenge for analytical scientists. This article examines the chemical aspects and strategies used to analyse this compound over time. Many times, the harmful effects of drug of abuse are exacerbated by its impurities. This is precisely the case with the drug under consideration here. Scientists have been interested in Methamphetamine impurity profiling for a long time, and a chronicle of it has been presented here.

1. Introduction

Methamphetamine is a stimulant and extremely addictive substance. It is an N-methylated derivative of amphetamine with similar characteristics and a similar mode of action. Dopamine is a neurotransmitter that is produced in large quantities in the brain as a result of methamphetamine use. Dopamine has a role in pleasure, motivation, reward, and motor function. Methamphetamine rapidly triggers the release of dopamine in activating sections of the brain leading to a euphoric "rush" or "flash". Frequent use may lead to severe addiction.[1].



Methamphetamine

United Nations Office on Drugs and Crime (UNODC) has affirmed that amphetamine-like substances (ATS) on the illicit drug market, have overtaken cocaine and heroin combined.[2] Similarly, Cannabis and ATS are two major illicit drugs in Australia, trailing only [3]. Consumption of ATS, particularly methamphetamine, is rising in a major part of the Asian subcontinent.

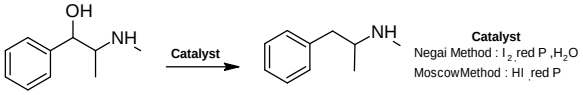
The following are some common methods for producing Methamphetamine from precursors such as phenyl-2-propanone (P-2-P), pseudoephedrine and ephedrine, 3,4-Methylenedioxyphenyl-2-propanone, and 4-methoxyphenyl-2-propanone. For the synthesis of Methamphetamine and 3,4-MethylenedioxyMethamphetamine (MDMA), a variety of methods such as the Nagai, "Moscow," and "Hypo" schemes, Emde method, The Leuckart method, Birch reduction, and Reductive amination are often used.[4].

Impurities formed during the synthesis of methamphetamine. This review examines the various types of impurities found in Methamphetamine, along with methods for profiling impurities such as gas chromatography, thermal desorption, liquid-liquid extraction by gas GCMS, capillary electrophoresis mass spectrometry, H1 NMR spectroscopy, and other techniques [5]

2. Synthetic Route for Manufacture Methamphetamine

A. The Nagai, "Moscow" and "Hypo" methods

The hydroxyl group of starting material is nucleophilically replaced by iodide in this technique, producing either iodoephedrine or iodopseudoephedrine. The Internal nucleophilic may cause the formation of cis- and trans-1,2-dimethyl-3-phenyl aziridines. These aziridine derivatives can undergo either reduction producing methamphetamine, or hydrolysis leading to P-2-P. P-2-P can condense in acidic conditions to form 1,3-dimethyl-2-phenyl naphthalene and 1-benzyl-3-methylnaphthalene. As a result, the possibility of two naphthalene by-products is route dependent. Importantly, one should understand that naphthalene is formed simply by heating P-2-P in the presence of acid for an extended period. Even reports of other naphthalene derivatives have been reported in other conditions. [8-11]

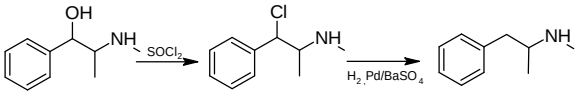


Scheme 1: Nagai and Moscow methods

Interestingly carbon at the 2-position of the propyl side chain is safe from nucleophilic attack hence the (S)-configuration of its centre is retained. [12]

B. The Emde method

In Southeast Asia, the Emde process has emerged as a well-known technique for large-scale synthesis. The Emde process, such as the Nagai process, includes halogenating ephedrine or pseudoephedrine and then hydrogenating it while preserving the chirality of the carbon-containing nitrogen. With the Emde process, the -OH group in starting material can be exchanged with chloride through the use of intramolecular nucleophilic substitution (also referred to as SNi substitution) or intermolecular substitution (SN_2 substitution).

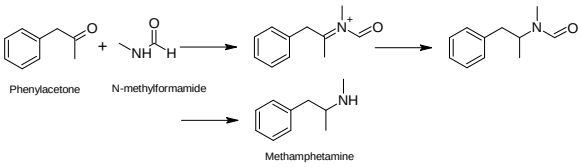


Scheme 2 : Emde method

While using thionyl chloride as the reagent, Lekskulchai et al. and Allen and Kiser proposed two routes. The latter group demonstrate that (-)-ephedrine produces a 99:1 mixture of (+)-chloropseudoephedrine and (-)-chlorefedrine, and (+)-pseudoephedrine produces a 6:4 mixture, while there is no difference between the chlorination products (+)-pseudoephedrine and (-) (approximately 1:1 chloride mixtures). The SNi substitution reaction was found to be more prominent in (+)-norpseudoephedrine, (-)-methyl ephedrine, and (+)-methyl pseudoephedrine as the extent of N-methylation enhanced.[13, 14] Both Allen and Kiser [14] and Barker and Antia [15] used nuclear magnetic resonance spectroscopy (NMR) and gas chromatography-mass spectrometry (GC-MS) for the characterization of reaction products.

C. The Leuckart method

The Leuckart reaction or Leuckart Wallach reaction is an important reaction for the synthesis of ATS because it can be employed to synthesise a variety of amphetamines derivatives using easily available reagents. Leuckart first described the reaction in 1885[6] using ammonium formate or formamide and Wallach expanded on it in 1893 using ammonium formate or formamide, and later in the presence of excess formic acid.[7]



Scheme 3 : Leuckart methods

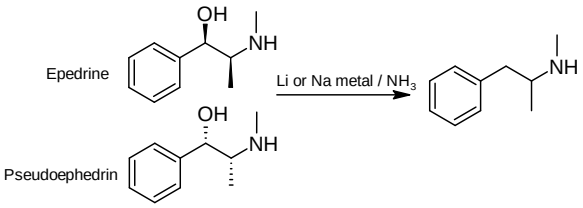
The key intermediate in the Leuckart approach to creating methamphetamine is N-formyl methylamphetamine. According to Kram and Kruegel[16], illegal Methamphetamine prepared by the Leuckart synthesis may contain N, N-di-(b-phenyl isopropyl)methylamine and N-formyl methylamphetamine. The latter among the two compounds might be route-specific. According to Sanger et al. [17], N-formyl methylamphetamine is route-specific for the Leuckart reaction. However, Qi et al. [18] and other groups[19, 20] have found N-formyl methylamphetamine, in very low

concentrations, in Methamphetamine produced by methods other than the Leuckart. Qi et al. noticed that the appearance of N-formyl methylamphetamine has been associated with the presence of N-acetyl methamphetamine, which was said to have resulted from a reaction between Methamphetamine and ethyl acetate. Conn et al. [21] were the first to report the coexisting N-acetyl methamphetamine in illicit Methamphetamine probably due to the use of propyl acetate to azeotropically desiccate Methamphetamine that had been precipitated out using aqueous HCl. Sasaki and Makino[22] demonstrate that the abundance of both N-formyl and N-acetyl-Methamphetamine rises with the temperature of the injection port increases, and they theorise that this phenomenon is caused by the thermal decomposition of an unknown compound(s) that decreases as you raise the temperature. Anyway, the presence of N-formyl methylamphetamine in minute amounts in seized Methamphetamine could be confusing and hence might require cautious interpretation.

Impurities in Methamphetamine[16, 23] can be detected if impure P-2-P, methylamine, or N-methyl formamide (probably containing dibenzyl ketone, ammonia, or formamide, respectively) are used in the Leuckart reaction. In addition to the earlier mentioned impurities, Kunulan[19] discovered dibenzyl, 3,4-diphenyl-3-butenone, benzyl methamphetamine, N-b-(phenyl isopropyl)benzyl methyl ketimine, N-benzoyl methamphetamine, benzylamphetamine, N-benzoyl methamphetamine, N-benzoyl methamphetamine (the latter demethylated by-products might have appeared from formamide in the N-methyl formamide employed).

D. The Birch reduction

Barker and Antia[15] discuss the consequences of starting with plant extracts from the genus Ephedra. It was envisaged that the methyl and desmethyl analogues of ephedrine and pseudoephedrine (e.g., methyl ephedrine and norephedrine) are reduced to amphetamine and dimethyl amphetamine, along with by-products 1,4-cyclohexadienyl-2-methylamino propane desmethyl and methyl analogues.

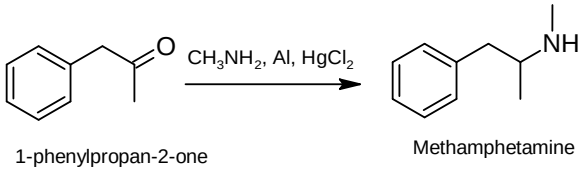


Scheme 4: Birch reduction

Per expectations, the 1,4-cyclohexadienyl moiety in 1-(1,4-cyclohexadienyl)-2-methylamino propane aromatises to form Methamphetamine. According to Pal et al, [24, 25] rapid aromatisation occurs in the soil, primarily through abiotic processes. Consequently, residues in soil samples from covert laboratories are devoid of 1-(1,4-cyclohexadienyl)-2-methylamino propane, even if it was previously detectable. Likewise, the oxidation of this diene may lead to the formation of Methamphetamine though it was not present from the beginning.

E. Reductive amination

Verweij[23] surveyed the reductive aminations of 1-phenylpropanoid-2-one in the presence of ammonia and methylamine. A common by-product of both was 1-phenyl-2-propanol, which results from the reduction of the starting material and hence was described as a route-specific by-product.



Scheme 5: Reductive amination

Salouros et al. [26] identified N-cyanoethyl-N-methyl-1-phenyl-2-propylamine as a route-specific impurity formed on reductive amination of 1-phenylpropanoid-2-one and methylamine.

Kunulan et al. [19] studied the impurities in Leuckart and reductive amination methamphetamines affirming Verweij's[23] discovery of 1-phenyl-2-propanol being a route-specific by-product.

3. Analytical methods for assay of Methamphetamine

A. Individual Analysis

For quantitative estimation of amphetamine and methamphetamine in different samples, a variety of analytical techniques such as titrimetric, spectroscopy, capillary electrophoresis, liquid chromatography, and gas chromatography have been employed. Without a doubt, the most viable tool for confirmation and identification is GC coupled online to an MS detection system. [27] The quest for non-destructive, simple, less analysis time, cost-effective, non-simple instruments, and less skilled technicians led to the development of the FTIR technique for in-situ detection and traces of methamphetamine. Riyanto et al utilised FTIR to identify wavenumber 698.83 cm-1, yielding an R2 value of 0.9998.[28] Hughes et al. curated a new quick and low-cost method using ATR-FTIR and PLS. The Root Mean Square Error of Prediction for this method was 3.8, R2 0.9779, and the lower LOQ was 0.7% of Methamphetamine. [29]

B. Trace Analysis

As a drug of abuse, it is essential to detect trace amounts of drugs in crime scenes, suspects, and biological samples. McKenzie et al invented a dynamic solid phase microextraction (SPME) attached with a field sampler capable of collecting enough samples in two hours and was followed by GC-MS. [30]

Though a successive review of biological sample analysis is expected, mention of analysis involving dried urine spot (DUS) analytical method based on spotting urine samples (10 µL) onto dried spot collection cards are made. The samples were analysed using extraction followed by the LC-MS-MS method with an r value greater than 0.995.[31]

C. Chiral separation

Another concern with methamphetamine is that it has a stereogenic centre and thus exists as an enantiomer. Both enantiomers have distinct pharmacological activities. As a result, developing enantioselective analysis was critical. Jirovska et al. reviewed several chiral separation methods.[32] They discussed different methods such as gas chromatography, high-performance liquid chromatography, high-performance capillary electrophoresis, as well as immunoassay in this review. Later that year, Li demonstrated super critical chromatography-single quadrupole mass spectrometry (SFC-SQD) for determining methamphetamine enantiomers. For optimal separation, a Trefoil AMY1 (150 x 2.1 mm, 2.5 m) column with a supercritical CO_2 mobile phase containing ethanol as the co-solvent and 1% cyclohexylamine as the amine additive was found to be ideal.[33]

D. Pharmacokinetics and Metabolism studies

Methamphetamine primarily metabolizes to amphetamine and 4-hydroxy methamphetamine[34] by human CYP2D6 and, to a lesser extent, CYP3A4 [35]. Amphetamine further metabolizes to 4-hydroxy methamphetamine and norephedrine by CYP2D6 [34, 36]. In most cases, GC-MS was used in these studies. Earla and co-workers while working with the same studies on Rhesus Macaque, developed and validated a very sensitive analytical method with liquid chromatography with tandem mass spectrometry (LC-MS/MS) method with sample preparation involving solid phase extraction of rhesus plasma. The method had a LOQ of 1.09 ng/ml for Methamphetamine and its metabolites, 4-hydroxy Methamphetamine, amphetamine, 4-OH amphetamine, and norephedrine.[37]

E. Bioanalysis

This discussion is in continuation of the earlier section**.** Campíns-Falcó et al [38] reviewed the analysis of amphetamine and Methamphetamine by HPLC. A comparison of the Fluorescence polarization immunoassay (FPIA) method, Radioimmunoassay (RIA) and GC–MS for blood samples has been reported.[39] Moellera et al, have presented an excellent review on the determination of Methamphetamine in blood. A tabular comparison of various chromatographic methods for the analysis of Methamphetamine can be found in this review. [40] In this regard, it is necessary to mention a US patent issued in 1992 by Heiman et al. It primarily makes use of the Fluorescence Polarization Immunoassay.[41]

There are many citations of analysis of urine samples for methamphetamine. [42, 43]. This includes a method involving derivatization for better detection in HLPC. [42 44-46]. Few are highly sensitive to trace concentration in a hair sample. [42, 47]

F. Simultaneous determinations

Another challenge for analytical scientists was developing and validating methods for various drug combinations. Methamphetamine has been marketed in numerous combinations with other drugs. Shabir et al. developed an RP-HPLC Method for the Determination of Methamphetamine and Propranolol in Tablet Dosage as an example.[48]

Illicit drug combinations pose an additional challenge to analysts; for example, an amphetamine, methamphetamine, caffeine, paracetamol, and theophylline combination was discovered in detained drugs in Riyadh, where Sultan et al. developed an analytical method.[49]

The problem multiplies when analysing the concentration of Methamphetamine in samples from drug addicts because they frequently use multiple substances in combination. One earlier referred article by Kim *et. al* [47], is representative of such a case where the group had successfully developed a method for the simultaneous analysis of 13 different drugs. Another instance is Chan et al's method for estimation of Methamphetamine in a beverage intoxicated with Methamphetamine, 3,4-methylenedioxyMethamphetamine and Ketamine.[50].

4. Impurity Profiling of Methamphetamine

Methamphetamine involves impurities which made the drug intolerable. Ira S. Lurie et al [51] performed impurity profiling of Methamphetamine using High-performance liquid chromatography (HPLC) with photodiode array (PDA) UV and fluorescence (FL) detection, and capillary electrochromatography (CEC) with laser-induced fluorescence (LIF) detection for analysis of acidic extracts derived from Methamphetamine. HPLC with conventional FL detection provided at least a 600 times increase in sensitivity over UV detection for certain of these solutes. The use of a fast scanning FL detector (with "on the fly" excitation or emission acquisition) provided structural information as well as "optimal" excitation and emission detection wavelengths. CEC with LIF detection via UV laser excitation provided significantly enhanced accuracy chromatographic technique over HPLC, with ng/ml detection limits.

Hiroyuki Inoue et al [52] went on to classify seized Methamphetamine through impurity profiling and established that it can furnish valuable information in criminal investigations of drug traffic routes, sources of supply and relationships between confiscations. They investigated a sample size of 50 mg sample of Methamphetamine HCl dissolved in phosphate buffer. Extraction using ethyl acetate with four internal standards (ISs) (n-decane, n-pentadecane, n-nonadecane, and n-hexacosane) was followed by gas chromatography (GC). Efficient separation was observed with the middle bore size column. The four internal standards helped for correcting impurity peak retention. The correction of impurity peak retention times with four ISs resulted in precise peak identification for subsequent data processing. After performing a logarithmic transformation, the statistical analysis was done using the Euclidean distance of the relative peak areas, and twenty-four characterizing peaks were chosen to enable comparison and the assessment of sample similarity and/or dissimilarity. According to the findings, it is possible to profile methamphetamine impurities using the current methodology.

Y. Marumo et al. [53] employed atomic absorption spectrometry(AAS) and inductively coupled plasma mass spectrometry (ICP-MS) to evaluate the effectiveness of inorganic impurity analysis in detecting samples of methamphetamine that had been confiscated in Japan. Triplicate aliquots from the 17 methamphetamine samples were used for qualitative analysis, employing water as solvent. Inorganic entities like Ba, Br, Cu, Pd, Sb, Sr, and Zn were determined using the ICP-MS, while Na was determined using the AAS. The contents of both Na and Br presented relatively lesser intra-sample variance despite being abundant in methamphetamine samples. ICP-MS qualitatively

identified trace elements as Au, Cs, Hg, and Tl. The fact that these components were consistent throughout all the confiscated samples, impurity profiling was made possible. One can conduct highly sensitive analyses due to ICP-MS and AAS. By employing these methods for the study of inorganic impurities, methamphetamine that has been seized can be profiled for impurities using organic impurity analysis.

By contrasting the impurity patterns of methamphetamine samples made using various synthesis techniques, Jae Sin Lee et al.[54], discovered the impurities reflecting the conditions of synthesis. Ephedrine and pseudoephedrine were converted into sixteen samples of methamphetamine using the three different production processes used in Emde, Nagai, and Moscow. After synthesising the sample, they extracted it using ethyl acetate that contained four internal standards and then used GC-MS and GC-FID to look into the patterns in the organic impurities. The final 10 peaks from the GC chromatogram relate to the synthetic methods employed. The regions of the chosen peaks were transformed into variables appropriate for statistical analysis, and the resulting cluster analysis allowed the synthesised samples to be divided into four groups. The appearance of the impurities was influenced by reaction conditions including pH, catalyst, and intermediates. The impurities were dimers derived from aziridine compounds, 1-phenyl-2-propanone, or other very reactive impurities.

Kenji Kuwayama et al[55] used thermal desorption (TD) and gas chromatography-mass spectrometry for impurity profiling of methamphetamine using GC–MS. Impurities from nine different batches were removed and separated using TD/GC-MS under diverse circumstances. The best chromatograms were recorded when a 20 mg sample of methamphetamine was extracted using a TD instrument at 120°C for 3 minutes. The extracts then were separated using a non-polar capillary column covered by (5%phenyl)-methylpolysiloxane. Without the need for a time-consuming extraction technique, methamphetamine-related substances such as amphetamine, benzaldehyde, benzyl alcohol, cis- and trans-1,2-dimethyl-3-phenyl aziridine, dimethylamphetamine, and N-acetyl ephedrine were detected in the chromatograms. Without the need for a time-consuming extraction technique, methamphetamine-related substances such as benzaldehyde, benzyl alcohol, amphetamine, cis- and trans-1,2-dimethyl-3-phenyl aziridine, dimethylamphetamine, and N-acetyl ephedrine were found in the chromatograms. Sample intensities varied from sample to sample. The impurity profile of methamphetamine via TD and liquid-liquid extraction (LLE) were studied. Higher intensities & numbers of peaks were found with TD, however, LLE provided greater resolution. They noticed that TD allowed for more effective solvent extraction.

The revolutionary step in methamphetamine profiling by Ying Qi et al. [56] involves the identification of the primary, route-specific flag impurity compounds. Fresh crystalline methamphetamine, also referred to as "ice," was seized by the Australian Federal Police in 2003 and 2004 at the Australian border. The impurity analysis of this sample produced markers for two different synthesis routes in the form of chemicals. Impurities typical of the Leuckart method and/or reductive amination were also present, along with 1,2-dimethyl-3-phenyl aziridine, 1,3-dimethyl-2-phenyl naphthalene & 1-benzyl-3-methylnaphthalene, alongside N-formyl methamphetamine, N, N-di-(β-phenyl isopropyl)amine and N, N-di-(β-phenyl isopropyl) methylamine, N-benzoyl amphetamine and N, N-di-(β-phenyl isopropyl)formamide commonly associated with the Leuckart route and/or reductive amination.

According to, Vanitha Kunalan[57] and the group's studies, impurity profiling of methamphetamine seizures can offer a wealth of information for forensic investigations, notably regarding drug trafficking routes, sources of supply, and connections between confiscations. It is particularly crucial to identify "route specific" contaminants or those that reveal the synthetic procedure utilised in illegal laboratories. They compared the contaminants in methamphetamine

produced internally using the Leuckart and reductive amination processes from the same starting material (P2P). With extraction using a basic buffer of pH 10.5, R, R-dimethyl diphenethylamine and N-R, R-trimethyldiphenethylamine we identified while. In the acidic media, at pH 6, 1-phenyl-2-propanol, was identified as a route-specific impurity.

Jaesin Lee et al.[58] used liquid-liquid extraction (LLE) and headspace solid-phase microextraction (HS-SPME) techniques to analyse 48 impurities in Methamphetamine samples. They used an MPS-2 autosampler and internal standard nonadecane (C19) diluted with potassium bromide (KBr) to improve the reproducibility. The SPME method identified impurities in a different pattern than the LLE method. The SPME method did not identify non-volatile impurities such as methamphetamine dimer, but it did reveal some volatile impurities such as diphenylketone, caprolactam, and many unknown factors. They discovered that the peaks of 1-phenyl-2-propanone (P2P), 1-phenyl-2-propanol, and benzyl cyanide could be differentiated by the SPME method with the least noise from amphetamine and methamphetamine degradants. They conclude that automation and the use of IS enabled them to perform multisampling analysis by the SPME method with high reproducibility, and cross-examination of the LLE and SPME methods improved the reliability of profiling results. The improved reliability of profiling results aided in the efficient investigation and regulation of methamphetamine and related chemicals, resulting in a lowering in methamphetamine abuse.

T. Mikuma et al[59] developed chiral capillary electrophoresis/tandem mass spectrometry (CE/MS/MS) using a chemically modified capillary containing sulfonated groups for amphetamine-type stimulants (ATS) viz; amphetamine, methamphetamine, norephedrine, or pseudoephedrine, ephedrine, pseudoephedrine, dimethylamphetamine and methyl ephedrine. A buffer system of 10 mM formic acid was used, along with a chiral selector of 20 mM highly sulphated—cyclodextrin (pH 2.5). They were able to resolve all 16 enantiomers in 60 minutes and correctly determine them due to their distinct mass spectra. Furthermore, the RSDs of the analytes' migration periods were less than 0.3% in the absence of any standardisation. They prepared a highly concentrated solution of methamphetamine (1 mg/mL) and added (1R,2S)-(-)-EP and (1S,2S)-(+)-Pseudoephedrine, which are considerable ATS impurities originating in the precursors, to it. They finally evaluated the mixture as mock samples for methamphetamine impurity analysis, and they noted acceptable repeatability of the migration times of (-)-E The limits of detection (LOD) for (-)-Ephedrine and (+)-Pseudoephedrine were estimated to be approximately 0.2% because their LOD as impurity values were around 2 g/mL. These techniques were used to analyse samples of methamphetamine that had been confiscated and had been highly concentrated (1 mg/mL) in water. Both (-)-Ephedrine and (+)-Pseudoephedrine might be detected, and they had equivalent migration periods and mass spectral patterns. The advantage of higher reproducibility and simplicity are two important aspects of this work.

In a work by Hun Joo Lee et al. [59], they described a visual peak selection system (VPSS) in conjugation with impurity profiling and used a newly developed normalising method for multi-Internal Standards (ISs) to improve the resolution of impurity peaks. They used relative retention time (RRT) as a criterion for classifying numerous chromatographic peaks for drug impurity profiling. Unfortunately, it was found that the classification of each chromatographic peak was challenging because RRT values ranged from 0 to 1, and tended to converge to 1 as the number of impurities in the sample increased, and accuracy was also low. A new visual peak selection method with a normalisation algorithm was developed to address the issue. By extending the range of the chromatogram, it successfully separated each chromatographic peak.

It might be a helpful tool for analytical samples with high impurity and IS concentrations. They found that impurity profiling had significantly

improved in terms of resolution, accuracy, speed, and user-friendliness.

Sanggil Choe et al [60] analysed 126 detained samples of Methamphetamine with GC-MS. All chromatogram peaks were analysed resulting in the identification of 61 impurities, including n-octacosane. Flunarizine and desloratadine, two pharmaceutical medicines, were found in crystalline Methamphetamine in different cases. The ORI, LOQ, and SQRT for data sets were reported in support.

5. Conclusion

The case of methamphetamine posed a significant challenge not only to synthetic chemists, druggists, and pharmacologists but also to analytical chemists. It was an ideal case with a variety of issues, but analytical scientists played a role in the identification, characterization, and forensic findings. Because there had been so much good work done, this review could only provide a brief overview.

6. Acknowledgments

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7. Conflict of interest

The authors declare there is no conflict of interest.

8. Bibliography

1. World Drug Report 2012. https://www.unodc.org/unodc/en/data-and-analysis/WDR-2012.html.
2. Drug statistics and trends. https://www.unodc.org/unodc/en/data-and-analysis/WDR-2010.html.
3. ATS: second most commonly abused drug type worldwide. https://www.unodc.org/unodc/en/frontpage/2011/September/ats-second-most-used-drug-type-in-the-world.html.
4. Lee, J.; Han, E.; Lee, S.; Kim, E.; Park, Y.; Lim, M.; Chung, H.; Park, J., Analysis of the impurities in the methamphetamine synthesized by three different methods from ephedrine and pseudoephedrine. *Forensic science international* 2006, *161*, 209-15.
5. *Economic and Social Consequences of Drug Abuse and Illicit Trafficking*; 1998.
6. Leuckart, R. J. B. d. d. c. G., Ueber eine neue Bildungsweise von Tribenzylamin. 1885, *18* (2), 2341-2344.
7. Wallach, O. J. J. L. A. d. C., Zur Kenntniss der Terpene. 1888, *245* (3), 241-278.
8. Skinner, H. F. J. F. s. i., Methamphetamine synthesis via hydriodic acid/red phosphorus reduction of ephedrine. 1990, *48* (2), 123-134.
9. Cantrell, T. S.; John, B.; Johnson, L.; Allen, A. J. F. S. I., A study of impurities found in methamphetamine synthesized from ephedrine. 1988, *39* (1), 39-53.
10. Allen, A. C.; Stevenson, M. L.; Nakamura, S. M.; Ely, R. A. J. J. F. S., Differentiation of illicit phenyl-2-propanone synthesized from phenylacetic acid with acetic anhydride versus lead (II) acetate. 1992, *37* (1), 301.
11. Windahl, K.; McTigue, M.; Pearson, J.; Pratt, S.; Rowe, J.; Sear, E. J. F. s. i., Investigation of the impurities found in methamphetamine synthesised from pseudoephedrine by reduction with hydriodic acid and red phosphorus. 1995, *76* (2), 97-114.
12. Barker, W.; Antia, U., A study of the use of Ephedra in the manufacture of methamphetamine. *Forensic science international* 2007, *166* (2-3), 102-109.
13. Lekskulchai, V.; Carter, K.; Poklis, A.; Soine, W. J. J. o. a. t., GC-MS analysis of methamphetamine impurities: reactivity of (+)-or (−)-chloroephedrine and cis-or trans-1, 2-dimethyl-3-phenylaziridine. 2000, *24* (7), 602-605.
14. Allen, A. C.; Kiser, W. O. J. J. o. F. S., Methamphetamine from Ephedrine: I. Chloroephedrines and Aziridines. 1987, *32*, 953-962.
15. Barker, W. D.; Antia, U., A study of the use of Ephedra in the manufacture of methamphetamine. *Forensic Sci Int* 2007, *166* (2-3), 102-9.
16. Kram, T. C.; Kruegel, A. J. J. o. F. S., The Identification of Impurities in Illicit Methamphetamine Exhibits by Gas Chromatography/Mass Spectrometry and Nuclear Magnetic Resonance Spectroscopy. 1977, *22*, 40-52.
17. Sanger, D. G.; Humphreys, I. J.; Joyce, J. R., A review of analytical techniques for the comparison and characterization of illicit drugs. *J Forensic Sci Soc* 1979, *19* (1), 65-71.
18. Qi, Y.; Evans, I.; McCluskey, A., New impurity profiles of recent Australian imported 'ice': methamphetamine impurity profiling and the identification of (pseudo)ephedrine and Leuckart

specific marker compounds. *Forensic Sci Int* 2007, *169* (2-3), 173-80.
19. Kunalan, V.; Nic Daeid, N.; Kerr, W. J.; Buchanan, H. A.; McPherson, A. R., Characterization of route specific impurities found in methamphetamine synthesized by the Leuckart and reductive amination methods. *Anal Chem* 2009, *81* (17), 7342-8.
20. Caldicott, D. G. E.; Pigou, P. E.; Beattie, R.; Edwards, J. W., Clandestine drug laboratories in Australia and the potential for harm. 2005, *29* (2), 155-162.
21. Conn, C.; Dawson, M.; Baker, A. T.; Keegan, J.; Fryirs, B., Identification of n-acetylmethamphetamine in a sample of illicitly synthesized methamphetamine. *J Forensic Sci* 1996, *41* (4), 645-7.
22. Sasaki, T.; Makino, Y., Effective injection in pulsed splitless mode for impurity profiling of methamphetamine crystal by GC or GC/MS. *Forensic Sci Int* 2006, *160* (1), 1-10.
23. Verweij, A. M., Impurities in Illicit Drug Preparations: Amphetamine and Methamphetamine. *Forensic Sci Rev* 1989, *1* (1), 1-11.
24. Pal, R.; Megharaj, M.; Kirkbride, K. P.; Naidu, R., Fate of 1-(1',4'-cyclohexadienyl)-2-methylaminopropane (CMP) in soil: route-specific by-product in the clandestine manufacture of methamphetamine. *Sci Total Environ* 2012, *416*, 394-9.
25. Pal, R.; Megharaj, M.; Naidu, R.; Klass, G.; Cox, M.; Kirkbride, K. P., Degradation in soil of precursors and by-products associated with the illicit manufacture of methylamphetamine: implications for clandestine drug laboratory investigation. *Forensic Sci Int* 2012, *220* (1-3), 245-50.
26. Salouros, H.; Collins, M.; Tarrant, G.; George, A. V., N-cyanomethyl-N-methyl-1-(3',4'-methylenedioxyphenyl)-2-propylamine: an MDMA manufacturing by-product. *J Forensic Sci* 2008, *53* (5), 1083-91.
27. *Recommended Methods for the Identification and Analysis of Amphetamine, Methamphetamine and their Ring-substituted Analogues in Seized Materials*; United Nations Office on Drugs and Crime: 2006.
28. Riyanto; Nas, S. W., Validation of Analytical Methods for Determination of Methamphetamine Using Fourier Transform Infrared (FTIR) Spectroscopy. *IOSR J. Pharm & Biol. Sci.* 2016, *11* (5), 51-59.
29. Hughes, J.; Ayoko, G.; Collett, S.; Golding, G., Rapid quantification of methamphetamine: using attenuated total reflectance fourier transform infrared spectroscopy (ATR-FTIR) and chemometrics. *PLoS One* 2013, *8* (7), e69609.
30. McKenzie, E. J.; Miskelly, G. M.; Butler, P. A., Detection of methamphetamine in indoor air using dynamic solid phase microextraction: a supplementary method to surface wipe sampling. *Analytical Methods* 2013, *5* (20), 5418-5424.
31. Chen, L.; Yu, Y.; Duan, G.; Wang, X.; Shen, B.; Xiang, P., Simultaneous determination of selegiline, desmethylselegiline, R/S-methamphetamine, and R/S-amphetamine on dried urine spots by LC/MS/MS: Application to a pharmacokinetic study in urine. *Frontiers in Chemistry* 2019, *7*.
32. Jirovsky, D.; Lemr, K.; Sevcik, J.; Smysl, B.; Stransky, Z., Methamphetamine--properties and analytical methods of enantiomer determination. *Forensic Sci Int* 1998, *96* (1), 61-70.
33. Li, L., Enantiomeric Determination of Methamphetamine, Amphetamine, Ephedrine, and Pseudoephedrine using Chiral Supercritical Fluid Chromatography with Mass Spectrometric Detection. *Microgram J.* 2015, *12* (1–4), 19-30.
34. de la Torre, R.; Yubero-Lahoz, S.; Pardo-Lozano, R.; Farre, M., MDMA, methamphetamine, and CYP2D6 pharmacogenetics: what is clinically relevant? *Front Genet* 2012, *3*, 235.
35. Welter, J.; Meyer, M. R.; Wolf, E. U.; Weinmann, W.; Kavanagh, P.; Maurer, H. H., 2-methiopropamine, a thiophene analogue of methamphetamine: studies on its metabolism and detectability in the rat and human using GC-MS and LC-(HR)-MS techniques. *Anal Bioanal Chem* 2013, *405* (10), 3125-35.
36. Miranda, G. E.; Sordo, M.; Salazar, A. M.; Contreras, C.; Bautista, L.; Rojas Garcia, A. E.; Ostrosky-Wegman, P., Determination of amphetamine, methamphetamine, and hydroxyamphetamine derivatives in urine by gas chromatography-mass spectrometry and its relation to CYP2D6 phenotype of drug users. *J Anal Toxicol* 2007, *31* (1), 31-6.
37. Earla, R.; Kumar, S.; Wang, L.; Bosinger, S.; Li, J.; Shah, A.; Gangwani, M.; Nookala, A.; Liu, X.; Cao, L.; Jackson, A.; Silverstein, P. S.; Fox, H. S.; Li, W.; Kumar, A., Enhanced methamphetamine metabolism in rhesus macaque as compared with human: an analysis using a novel method of liquid chromatography with tandem mass spectrometry, kinetic study, and substrate docking. *Drug Metab Dispos* 2014, *42* (12), 2097-108.
38. Campíns-Falcó, P.; Sevillano-Cabeza, A.; Molins-Legua, C., Amphetamine and methamphetamine determinations in biological

samples by high performance liquid chromatography. A review. *Journal of Liquid Chromatography & Related Technologies* 1994, *17* (4), 731-747.
39. Simonick, T. F.; Watts, V. W., Preliminary evaluation of the Abbott TDx for screening of D-methamphetamine in whole blood specimens. *Journal of analytical toxicology* 1992, *16* (2), 115-118.
40. Moeller, M. R.; Steinmeyer, S.; Kraemer, T., Determination of drugs of abuse in blood. *Journal of Chromatography B: Biomedical Sciences and Applications* 1998, *713* (1), 91-109.
41. Heiman, D. F.; Johnson, S. A.; Hu, H.-Y. Y., Method and reagents for detecting amphetamine and/or D-methamphetamine in biological samples. Google Patents: 1993.
42. Al-Dirbashi, O.; Qvarnstrom, J.; Irgum, K.; Nakashima, K., Simple and sensitive HPLC determination of methamphetamines in human urine as derivatives of 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoyl chloride, a new fluorescence derivatization reagent. *Biomedical Chromatography* 1999, *13* (2), 137-138.
43. Al-Dirbashi, O. Y.; Wada, M.; Kuroda, N.; Takahashi, M.; Nakashima, K., Achiral and chiral quantification of methamphetamine and amphetamine in human urine by semi-micro column high-performance liquid chromatography and fluorescence detection. *Journal of Forensic Science* 2000, *45* (3), 708-714.
44. Soares, M. E.; Carvalho, F.; de Lourdes Bastos, M., Determination of amphetamine and its metabolite p-hydroxyamphetamine in rat urine by reversed-phase high-performance liquid chromatography after dabsyl derivatization. *Biomedical Chromatography* 2001, *15* (7), 452-456.
45. Yamada, H.; Yamahara, A.; Yasuda, S.; Abe, M.; Oguri, K.; Fukushima, S.; Ikeda-Wada, S., Dansyl chloride derivatization of methamphetamine: a method with advantages for screening and analysis of methamphetamine in urine. *Journal of analytical toxicology* 2002, *26* (1), 17-22.
46. Foster, B. S.; Gilbert, D. D.; Hutchaleelaha, A.; Mayersohn, M., Enantiomeric determination of amphetamine and methamphetamine in urine by precolumn derivatization with Marfey's reagent and HPLC. *Journal of analytical toxicology* 1998, *22* (4), 265-269.
47. Kim, E.; Lee, J.; Choi, H.; Han, E.; Park, Y.; Choi, H.; Chung, H. In *Comparison of methamphetamine concentrations in oral fluid, urine and hair of twelve drug abusers using solid-phase extraction and GC-MS*, Annales de Toxicologie Analytique, EDP Sciences: 2008; pp 145-153.
48. Shabir, G. A., Development and Validation of RP-HPLC Method for the Determination of Methamphetamine and Propranolol in Tablet Dosage Form. *Indian J Pharm Sci* 2011, *73* (4), 430-5.
49. Sultan, M., Simultaneous HPLC determination and validation of amphetamine, methamphetamine, caffeine, paracetamol and theophylline in illicit seized tablets. *International Journal of Pharmacy and Pharmaceutical Sciences* 2014, *6* (4), 294-298.
50. Chan, K.-W.; Ramli, S. H., Development of an in-house HPLC method for the analysis of ecstasy-laced beverages. *Egyptian Journal of Forensic Sciences* 2018, *8* (1), 18.
51. Lurie, I. S.; Bailey, C. G.; Anex, D. S.; Bethea, M. J.; McKibben, T. D.; Casale, J. F. J. J. o. C. A., Profiling of impurities in illicit methamphetamine by high-performance liquid chromatography and capillary electrochromatography. 2000, *870* (1-2), 53-68.
52. Inoue, H.; Kanamori, T.; Iwata, Y. T.; Ohmae, Y.; Tsujikawa, K.; Saitoh, S.; Kishi, T. J. F. s. i., Methamphetamine impurity profiling using a 0.32 mm id nonpolar capillary column. 2003, *135* (1), 42-47.
53. Marumo, Y.; Inoue, T.; Seta, S. J. F. S. I., Analysis of inorganic impurities in seized methamphetamine samples. 1994, *69* (1), 89-95.
54. Lee, J. S.; Han, E. Y.; Lee, S. Y.; Kim, E. M.; Park, Y. H.; Lim, M. A.; Chung, H. S.; Park, J. H. J. F. s. i., Analysis of the impurities in the methamphetamine synthesized by three different methods from ephedrine and pseudoephedrine. 2006, *161* (2-3), 209-215.
55. Kuwayama, K.; Inoue, H.; Kanamori, T.; Tsujikawa, K.; Miyaguchi, H.; Iwata, Y.; Kamo, N.; Kishi, T. J. F. s. i., Contribution of thermal desorption and liquid–liquid extraction for identification and profiling of impurities in methamphetamine by gas chromatography–mass spectrometry. 2007, *171* (1), 9-15.
56. Qi, Y.; Evans, I.; McCluskey, A. J. F. s. i., New impurity profiles of recent Australian imported 'ice': methamphetamine impurity profiling and the identification of (pseudo) ephedrine and Leuckart specific marker compounds. 2007, *169* (2-3), 173-180.
57. Kunalan, V.; Nic Daéid, N.; Kerr, W. J.; Buchanan, H. A.; McPherson, A. R. J. A. c., Characterization of route specific impurities found in methamphetamine synthesized by the Leuckart and reductive amination methods. 2009, *81* (17), 7342-7348.

58. Lee, H. J.; Han, E.; Lee, J.; Chung, H.; Min, S.-G. J. F. s. i., Development of visual peak selection system based on multi-ISs normalization algorithm to apply to methamphetamine impurity profiling. 2016, *268*, 116-122.
59. Mikuma, T.; Iwata, Y. T.; Miyaguchi, H.; Kuwayama, K.; Tsujikawa, K.; Kanamori, T.; Inoue, H. J. F. S. I., The use of a sulfonated capillary on chiral capillary electrophoresis/mass spectrometry of amphetamine-type stimulants for methamphetamine impurity profiling. 2015, *249*, 59-65.
60. Choe, S.; Lee, J.; Choi, H.; Park, Y.; Lee, H.; Jo, J.; Park, Y.; Kim, E.; Pyo, J.; Lee, H. J. J. F. s. i., Estimation of the synthetic routes of seized methamphetamines using GC-MS and multivariate analysis. 2016, *259*, 85-94.