Impurity Analysis of MDA Synthesized from Unrestricted Compounds

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CERTIFICATE OF AUTHORSHIP/ORIGINALITY

I, Katherine Cooper declare that this thesis, is submitted in fulfilment of the requirements for the award of Master of Science (Research), in the School of Mathematical and Physical Sciences at the University of Technology Sydney. This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution. This research is supported by the Australian Government Research Training Program.

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Katherine Cooper
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List of Abbreviations

AFP	Australian Federal Police
ATS	Amphetamine type Stimulants
CNS	Central nervous system
DMA	Dimethylamphetamine
FTIR	Fourier transform infra-red spectroscopy
GC	Gas chromatography
GCMS	Gas Chromatography – Mass Spectrometry
HPLC	High Performance Liquid Chromatography
MA	Methamphetamine
MDA	3,4 methylenedioxyamphetamine
MDMA	3,4 methylenedioxymethamphetamine
MS	Mass spectrometry
NMR	Nuclear magnetic resonance spectroscopy
NPS	New Psychoactive Substances
PMA	*p*-methoxyamphetamine
PMMA	4-methoxymethamphetamine
2D DOSY	Two-dimensional diffused-ordered spectroscopy
2D-GC	Two-dimensional gas chromatography

Abstract

Methylenedioxyamphetamine (MDA) is classified as an illegal substance in many countries and jurisdictions around the world. Its popularity for illicit use is due to its stimulant and hallucinogenic effects. MDA can be synthesized from starting materials and reagents that are uncontrolled. These syntheses are attractive to clandestine laboratories as they can source large quantities of reagents without causing suspicion or risk of detection. Procedures for these syntheses require very little synthetic chemistry knowledge and are readily available online. Examination of the chemical profile of products from these syntheses can provide information about the starting material and synthetic pathway. This provides valuable information regarding linking cases, and tracking and limiting the supply of reagents used in clandestine laboratories.

This thesis examines the impurity profile of two synthetic pathways to MDA, from helional and piperonal, both of which involve few restricted compounds and would therefore be ideal to clandestine chemists. Helional is a fragrant oil available for wholesale purchase for home perfume makers and piperonal can be extracted from pepper. This thesis focuses on the organic impurities from side reactions between precursors, intermediates, and reagents, or reaction by-products. The products of each step were analysed using proton nuclear magnetic resonance spectroscopy (^{1}HNMR) and gas chromatography-mass spectrometry (GCMS). The results were examined to determine the identity of the impurities and to determine the presence of route specific impurities.

The results of this investigation show the identity of multiple impurities in the free base product of MDA synthesized from both helional and piperonal. Piperonal and MDP2P were shown to be common impurities between the syntheses. Most of the impurities identified within the helional product had been seen and recorded previously as impurities from other methods and none of the impurities carried through to the HCl product. Therefore, no route specific impurities were identified for the synthesis of MDA from helional.

1. Introduction

Illicit drugs and their use are a growing issue in society (1), the effects of which permeate beyond the user to the greater community. Habitual drug use has been shown to cause physical, relational, and mental health problems which in turn affects the user's friends and family (2). Of the illicit drugs present in society, amphetamine-type stimulants are the second most prevalent according to seizures, arrests, and use as a percentage of the population, only after cannabis (1). Law enforcement has come a long way with regards to illicit drugs since 1997 when the Australian Federal Police (AFP) started collecting information from profiling heroin. The AFP now have access to databases containing information about thousands of samples of different types of drugs that have been profiled. This program in combination with drug research centres around the world, has enabled a better understanding of trace impurities and how they connect to different geographical origins and synthetic pathways of the drug. Understanding the common synthesis routes of illicit drugs allows law enforcement agencies to track and limit the use of the precursor chemicals, reducing the amount purchased by, or redirected from legitimate industry use into the clandestine laboratories (3).

Ecstasy or 3,4 methylenedioxymethamphetamine (MDMA) is the most thoroughly studied and profiled amphetamine however 3,4 methylenedioxyamphetamine (MDA), a compound that is sometimes sold as ecstasy, has attracted far less research efforts into the impurities associated with its route of synthesis and resulting impurities. Chapter 1 of this thesis discusses prior research in the area of the analysis of these types of drugs especially research regarding chemical profiling and the information that can be gained through the identification of minor components and impurities.

1.1 Illicit Drugs in Society

Illicit drug use is a major problem within our globalised society and with the ease of the internet and international travel and post, the problem is only increasing despite global efforts to control and limit illicit drug supply. The United Nations Office of Drugs and Crime release an annual report on the global illicit drug trends with mortality statistics supplied by the World Health Organisation. In 2015 approximately 450,000 people died due to drug use, whether by, for example, overdose or diseases contracted through syringe use. In North America it was found that the life expectancy decreased for 2 consecutive years for the first time in 50 years. This is hypothesized to be somewhat caused by the increased use of fentanyl and fentanyl analogues which caused about 1/3 of all drug

overdose deaths in the United States in 2016. There has also been a sharp increase in both opium and cocaine production worldwide, increasing 65% and 25% respectively for the last measured year. Cannabis continued to be the most seized drug worldwide in both seizure number and weight even though it displayed a slight decrease, however the amount of cocaine and ATS seized worldwide in 2016 was a record high (4).

West, North, and Central Africa have become the hub for pharmaceutical opioid trafficking as it is responsible for 87% of the global seizures (4). With the rise of the opioid fentanyl in North America, much of Europe is still dominated by heroin and morphine with opioids accounting for 84% of drug deaths in 2016 (5). Methamphetamine is trafficked mainly through Asia and North America and has become the second biggest threat in the United States. It also continues to be a key concern in Asia and Oceania which has indicated a continually growing market for the drug (4).

1.2 Illicit Drugs in Australia

The Australian drug scene reflects the global one to some extent however there are some key differences in the drugs favoured by the Australian population. Like the global trend cannabis continues to be the most widely used drug in Australia; however, limited access to cocaine and heroin means lower use of these drugs compared to the international mean and higher use of ATS and New Psychoactive Substances (NPS) as compensation. An overview of data published in the annual Illicit Drug Report by the Australian Criminal Intelligence Commission, confirmed that illicit drug arrests and seizures, which indicate public involvement, have continued an upwards trend over the past 10 years (1). In the 2015-16 financial year there was a record 115,421 illicit drug seizures pertaining to over 20 tonnes of drugs, with 154,538 arrests for illegal drug activity. Cannabis continues to have the highest number of arrests as it has since 2005-2006. In this latest year it pertains to 51.6% of the drug related arrests with a total of 79,748. The second highest amount of arrests are related to Amphetamine type Stimulants (ATS) with 30.8% of the total (1). Figure 1 shows the percentage of total number of drug seizures in the same time period for the same drug type categories. Again, cannabis has the highest percentage with 53.1% of the total seizure number accounting for a total of 61,334 seizures, a 3% increase from the previous year. The second highest number of seizures is of ATS with 33.8% of the total number of seizures (1). Figure 2 shows the percentage of the total weight of drug seizures for each type with the highest being for ATS. 43.9% of the weight of drugs seized

was ATS with a total weight of 9,218 kg. The second highest percentage of the total weight is due to cannabis accounting for 28.9% of the total (1).

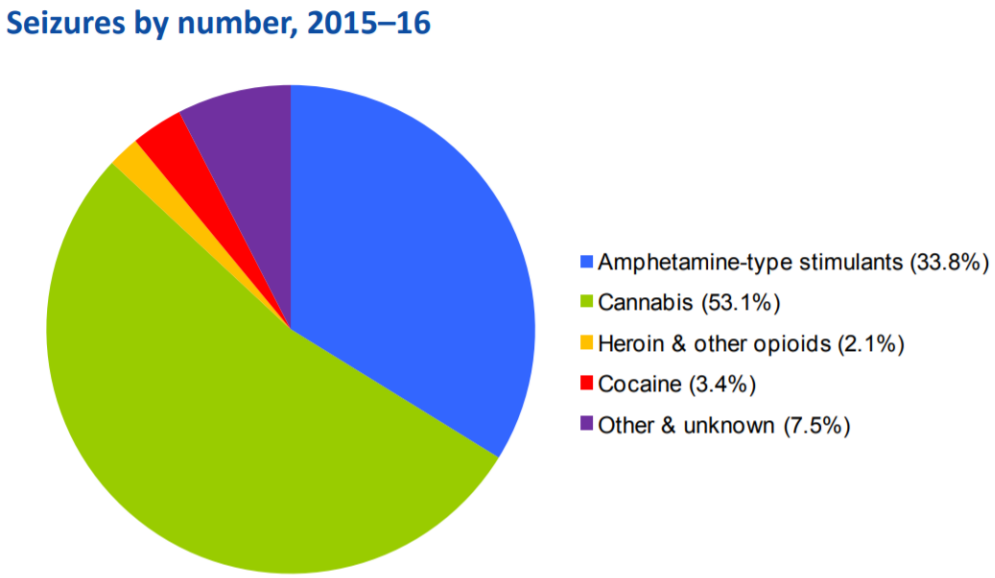


Figure 1: The total number of illicit drug seizures in Australia in the year 2015-2016 separated according to drug classification (1).

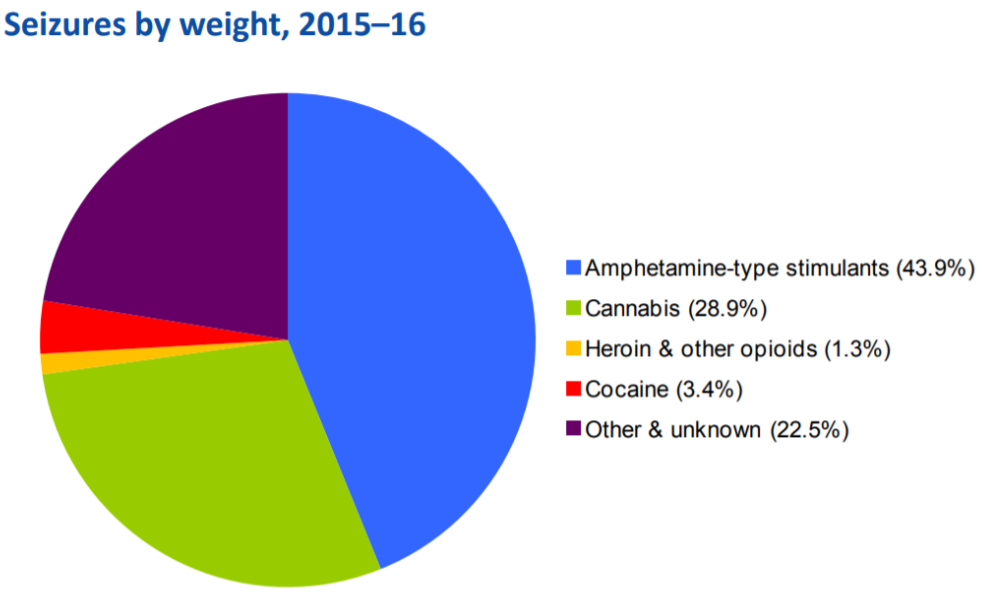


Figure 2: The total weight of all the drugs seized in Australia in the year 2015-2016 separated according to drug classification (1).

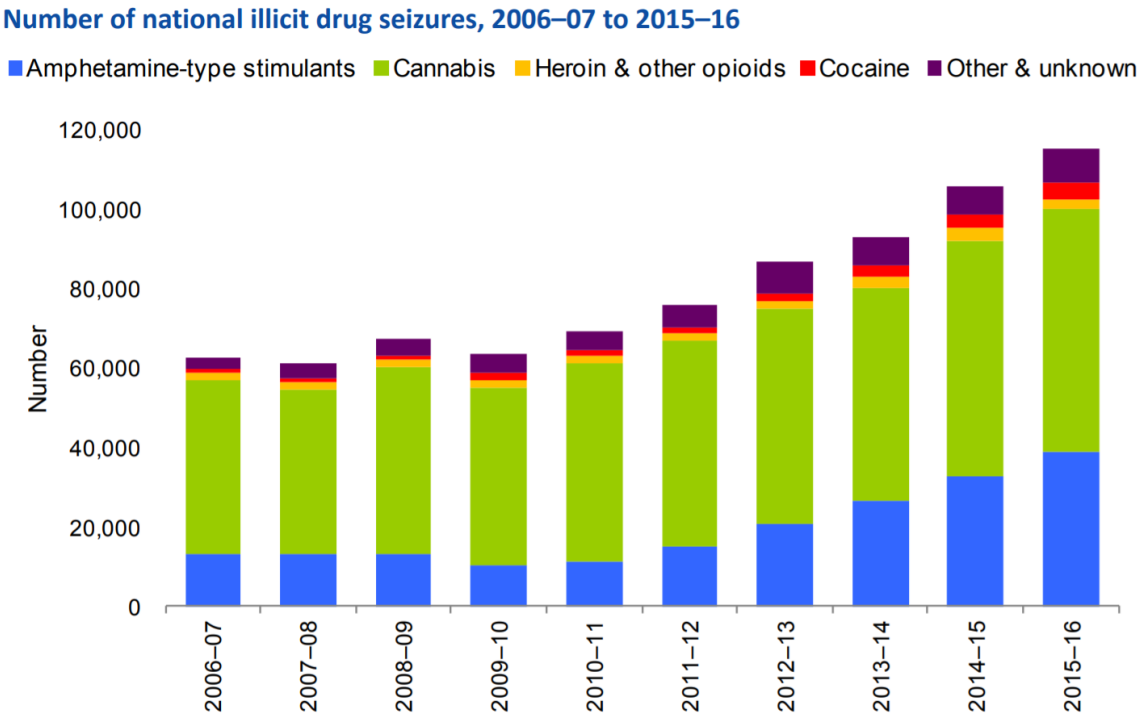


Figure 3: The number of illicit drug seizures in Australia per financial year from 2006 until 2016. Within each year the number of seizures are broken down according to drug type (1).

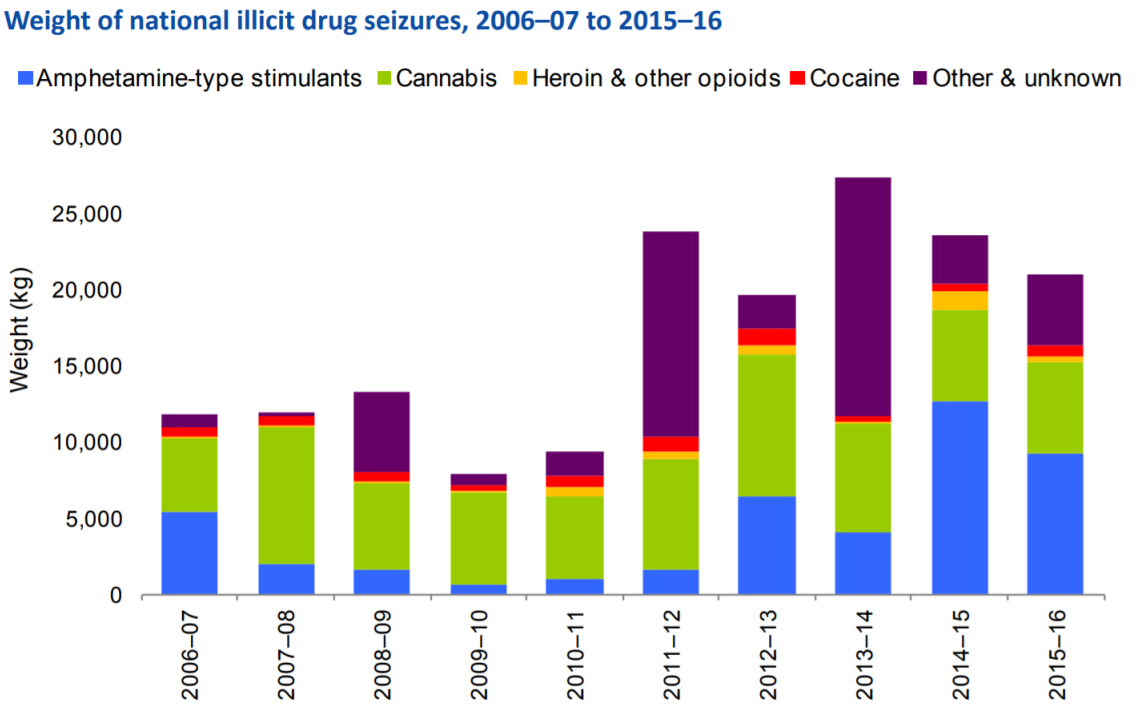


Figure 4: The weight of illicit drugs seized in Australia per financial year from 2006 until 2016. Within each year the weight of all seized drugs are broken down according to drug type (1).

More than half (50%) of the total arrests and seizures were for cannabis (**Error! Reference source not found.**), however by weight, the most drugs seized were amphetamine-type stimulants (Figure 2) which also had the second highest percent in regards to seizure number and arrests, pertaining to a little over 30% for both categories. Over the past 10 years there has been an increasing trend in drug related seizures by both number (Figure 3) and weight (Figure 4) with significant increases over the last 4 years. Cannabis, with the largest proportion of arrests and seizures has remained fairly constant over this time period however. ATS, which accounts for the second largest proportion, has more than doubled its arrests and seizures within the last 4 years after being fairly constant for the years previous to that. Cocaine and opioids have also doubled within the last 4 years; however they pertain to a much smaller amount of the drug market and therefore the effects are less noticeable (1).

Regarding problematic and illicit drug use, it is worth mentioning that in a lot of western countries there has been and still is a social pressure urging for the legalisation or at least decriminalisation of cannabis. If this were to pass in Australia it would mean that law enforcement agencies would not be troubled by the plant to the same degree and many illegal growers and suppliers, which make up the bulk of the statistics, could then obtain permits that would make their production of cannabis commercial and legal . However, no such movement exists for ATS use and supply, meaning that they will continue to be an issue for law enforcement agencies for far longer than cannabis, leaving them as the most problematic drugs in Australia in both arrests and seizures.

As seen in the data presented by the Illicit Drug Report, although cannabis is the most prevalent illicit drug in society, ATS presents a bigger threat due to the increase in these statistics. For the past four years arrests and seizures have been on a constant incline. In 2014-15, of the total weight of drugs seized, ATS accounted for 53.6% of them; this equals a record weight of 12.6 tonnes. There was less than half that weight in cannabis. In that same year there were more than 32 thousand seizures of ATS and this epidemic does not seem to be slowing down (1). In April 2017 there was the largest methylamphetamine seizure on record weighing a total of 903 kg.

The previous data showed the criminal aspects but there is a lot of illicit drug use that does not get detected. Another aspect to the data on drug use comes from surveys. A study by the University of New South Wales looked at the trends in drug use from 2001-2013.

This study classified the data into specific drug categories and looked at each individually. Interestingly the report found that the prevalence of the drugs and the percentage of people using the drugs was either remaining constant or declining towards the end of the timeline studied, with the exception of cocaine which has increased. However the proportion of people using that drug is still minimal compared to the others. Some questions must be asked of this nonetheless, when the data is compared with the previous data on seizures and arrests (6). Despite the recorded decline in drug use in recent years the National Rural Health Alliance reported that the percentage of people having used illicit drugs in the past year is still quite high with 15.3% of people over the age of 14 having used them. This increases to 18.8% of people when considering only remote areas of Australia (7).

The Illicit Drug Data Report also contained surveys that provide useful information into the Australian drug scene. The results of these surveys stated that the proportion of all Australians who have tried ecstasy in their lifetime has increased from 10.3% in 2010 to 10.9% in 2013. However, the proportion reporting recent use has decreased by 0.5% in the same time period to result in 2.5% of people having used ecstasy recently. Among drug users there seems to be a trend where more people are using ATS as opposed to other drugs. Of police detainees who undertook testing, 40.9% of them had a positive result for amphetamines; this is up 5% from the 2013-14 year and continues to be a higher proportion of people than those who test positive for every other drug except cannabis. All these studies show that, even though the percent of people who are recent users of ATS was on the decline in 2013, ATS are still prevalent throughout many cross sections of society. (1).

Recently a new way of measuring illicit drug use in a population has been developed. This is done by measuring the trace levels of these drugs and their metabolites in a city's wastewater. In Australia, this analysis has been carried out across South Australia and in Sydney (8, 9). In South Australia the use of MDMA and methylamphetamine was approximately 40 times higher compared to its use in European and American cities, which is a larger difference than would have been anticipated given the results of the voluntary surveys of drug use. The opposite is true of cocaine use across the cities with the wastewater analysis finding that European cities consume approximately 30 times the amount of cocaine per person than Adelaide. This result is much higher than the one that has been reported through the surveys (9). The wastewater analysis in Sydney also shows

the comparatively high rates of methylamphetamine and MDMA consumption compared to the use of other drugs in Sydney, and the use of methylamphetamine and MDMA in other cities (8). The data collected using this method, together with that available from surveys and seizures show the extent of the prevalence of amphetamines in Australian society.

1.3 Amphetamine-type Stimulants (ATS)

Amphetamines are a relatively new addition to the Australian drug market with methamphetamine (MA) only really gaining popularity in the late 1990's (10). This is due to the legislative change in the early 1990's that limited the availability of the main precursor amphetamine sulphate, which was previously the most readily available illicit ATS throughout the 1980's (11). The laws have continued to change since then, and chemists in clandestine laboratories have continued to adapt and create new ATS, thus there are now many different types of ATS readily available in today's society. Figure 5 shows the general structure of an ATS; they all include this structure at its core but with additional functional groups attached. This structure includes a benzene ring or phenyl group with a string of 2 carbons attached and then an amine group. Some more common drugs encountered include MA, MDMA and MDA. The structures of which are shown in Figure 6, Figure 7, and Figure 8 respectively.

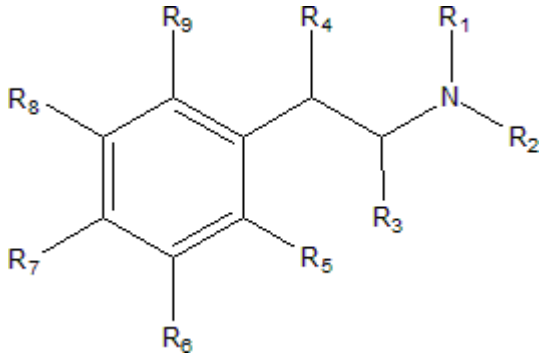


Figure 5: The general structure of all amphetamine-type stimulants

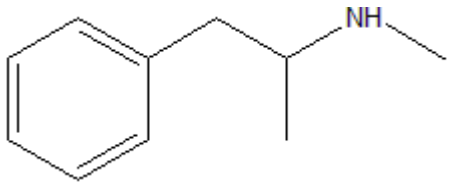


Figure 6: Structure of Methamphetamine (MA)

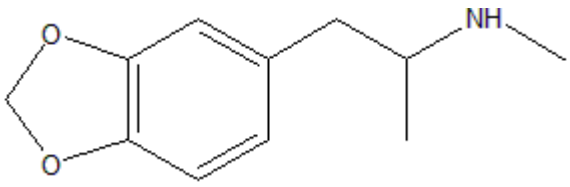


Figure 7: Structure of 3,4-methylenedioxymethamphetamine (MDMA)

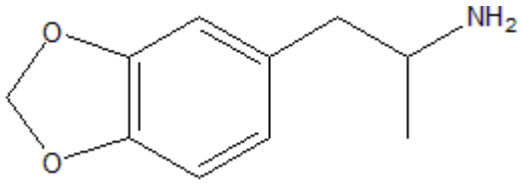


Figure 8: Structure of 3,4-methylenedioxyamphetamine (MDA)

1.3.1 Effects of ATS Use

ATS have a variety of both positive and negative effects on the human body. ATS stimulate the central nervous system (CNS) by increasing the levels of dopamine, serotonin, and noradrenaline in the brain. Different types of ATS affect these neurotransmitters at different levels; for example, MDMA increases the levels of serotonin more than the other neurotransmitters, whereas methamphetamine (MA) increases dopamine to a higher extent comparatively. Due to the variety in the resulting neurotransmitter levels the range of outward effects is quite large as well. Whereas MDMA results in mild hallucinations, euphoria and increased connection to others, MA results in increased confidence, energy, and libido (12). A study performed in 2010 investigated some proposed mechanisms behind drug-induced hallucinations from MDA, these being the loss of sensory or perceptual ability, abnormally increased neural activity, and alterations in cognitive functions (13). The study found that MDA causes the first two conditions mentioned but not the third, and these work together to induce hallucinations (for hallucinations are not a condition themselves but the result of the first two conditions mentioned). In the case of MDA the increased neural activity is an increase in serotonin levels as some of those specific receptors are inhibited (13).

Other desired effects can include reduced fatigue, enhanced reflexes, mood elevation, increased concentration and perceived increase in physical strength. Also small infrequent doses can improve fine motor skills and cognition; however results can quickly turn negative if the dose or length of use is increased (12).

Along with those effects that are desired by users comes a range of adverse side effects that are long term, short term, physical and mental. Some short term effects of ATS use include anxiety, insomnia, irritation, confusion, tremors, abdominal pain, muscle cramps, and increased heart rate (12). More serious effects of ATS use include sleep disorders, paranoid hallucinations, confusion, psychosis, agitation, severe panic, anxiety and depression (12). A study from Victoria found that people who use ATS are about twice as likely to have anxiety and depression. The study found that 85% percent of ATS users had experienced these mental illnesses during their lifetime, compared to 45% of the general population (12, 14).

Another very serious effect of ATS use has been found in multiple studies looking at the link between ATS use and psychosis. Human experiments found that states of psychosis can reliably be induced by ATS use in people with no genetic history of mental illness (12).

Along with the many psychological effects of ATS use there are also numerous physical consequences. A lot of the major effects have to do with the cardio-vascular system; for example, any use of the drug increases heart rate and blood pressure. Then after short term use, users can experience constriction of blood vessels and even cardiac arrhythmia. Some more serious effects of ATS include heart attack, stroke, aneurysm, and haemorrhaging; acute coronary syndrome is not uncommon among users admitted to hospital for chest pain. Along with cardiovascular problems ATS use also inhibits the body's ability to regulate and maintain the right body temperature; this leads to many users experiencing hypo/hyperthermia. Amphetamines are also appetite suppressants. Problems that arise from this are users losing weight and general poor nutrition; this includes high sugar diets which have an effect on their teeth. This lack of care and habitual grinding of teeth, another unrelated symptom of ATS use, causes terrible dental problems and makes people look older than their chronological age (12).

1.4 Profiling

The chemical profiling of illicit drugs can provide useful information to law enforcement agencies as they can contain many other organic by-products and impurity which can provide useful information. The chemical profile first and foremost tells investigators what is in a substance, and if an illicit compound is present or not, thus determining whether a crime has been committed. Then the identity of the constituents of a sample

can help to determine its origin ideally leading to the arrest and conviction of the person/s responsible for the supply of the illicit drug. Chemical profiling can be used in the criminal process, where it provides information for the court in order to convict someone. It can also be used to gather information, that can then potentially be used for forensic intelligence purposes. It can uncover links between specimens and seizures that were otherwise invisible; it can also distinguish between two otherwise identical looking specimens. Discovering this information helps uphold justice ensuring that the correct person is held responsible for each instance of drug trafficking. This is an important part in disrupting the drug market (15).

1.5 Analytical techniques

In today's technologically advanced society there are a myriad of instrumentation available that provide useful information regarding the chemical profiling of illicit substances. Many of them have very high discriminating power and are used to measure individual chemical characteristics of the various compounds allowing for their identification with statistical significance and certainty (16). However, due to the characteristics that they measure some are more useful, or more optimized for chemical profiling than others. The ability of an instrument to deal with complex mixtures is very important when analysing illicit drug samples as very rarely are samples pure. Some other practical aspects of the analysis to consider when undergoing chemical profiling are things such as sample preparation needed, sample analysis duration, and instrument cost. All these aspects are addressed in the studies mentioned in the following sections.

Infrared spectroscopy, gas chromatography-mass spectrometry and nuclear magnetic resonance are some of the most common analytical methods used in chemical profiling of illicit drugs. All these techniques measure the desired property to such a degree of precision that by combining the results a positive identification can be made of a compound to the exclusion of all others.

1.5.1 Fourier Transform Infra-Red Spectroscopy

Fourier transform infra-red spectroscopy (FTIR) is a presumptive test that can be performed in order to confirm the main constituent of a substance, which is very helpful within the context of illicit drug analysis for the purpose of determining whether a crime has occurred or not. Although this technique is limited in the information it is able to give, it is still very useful as a presumptive analysis. It's a fast analysis taking about a minute

per sample and requires little to no sample preparation. For the analysis of mostly pure substances the resulting spectra from the FTIR can be cross-checked with a database for a potential match which can be used to identify the main constituent (17).

A study performed by researchers at the University Sains Malaysia examined the use of this analytical technique for the profiling of 155 heroin samples seized by the Royal Malaysia Police between 2012 and 2015. After completing principle component analysis and hierarchic cluster analysis they concluded that this method of analysis was capable of discriminating the samples and grouping the samples according to similarities. By using reference samples of common cutting agents, the adulterants of some were able to be identified and the samples could be linked according to these additions. However the study concluded it is more of a linking and matching tool as opposed to an identification tool, they were able to link samples based on the spectra differences created by the individual impurities in each sample but were unable to identify what those compounds are, however these links are still useful to law enforcement agencies dealing with the illicit drug trade (18).

Another study in Brazil analysed 513 seized cocaine samples by FTIR to determine whether base cocaine could be differentiated from salt (crack) cocaine. The study found that for all the samples, the cocaine form was correctly identified. The hierarchical cluster analysis and principle component analysis on the data lead to the conclusion that FTIR is a reliable method of differentiating between crack cocaine and the base form. The study also found that it was possible to group samples according to the possibility of the same refining process or adulteration pattern as sharing these characteristics result in similar spectra, however further analysis is needed to either confirm or refute these particular links made as FTIR is not conclusive in this aspect (19).

In regard to impurity profiling of synthetic compounds for route specific impurities this technique is not a suitable method of analysis as it is incapable of separating the signals of one compound from the signals of another and therefore incapable of identifying the minor constituents of a substance.

1.5.2 Gas Chromatography – Mass Spectrometry (GCMS)

The most commonly used analytical method is gas chromatography (GC) normally coupled with a mass spectrometer (MS). This is a very useful analytical technique as it is able to separate out the components of a mixture and then provides information about

each component allowing its identification. GCMS provides more information than FTIR in that it is able to separate out a sample into the individual constituents giving a peak on the chromatograph with a retention time. For each peak it then records the mass spectrum. Using both the retention time and the mass spectrum an identity can be given to a particular constituent (20). This is very useful in chemical profiling for route specific impurities. However, samples need more preparation to be run through GCMS analysis than they do for FTIR, it also takes a lot longer to run each sample with run times ranging from 15-40 minutes each. Another potential problem with GCMS is that similar compounds are not completely separated out, so what appears to be one large peak on the chromatograph could, in fact, be two or more smaller peaks that have overlapped (21).

A 2002 study performed in France with seized MDMA ecstasy tablets verified the benefit of using GC in the context of illicit drug analysis. With the resulting chromatographs from the study they were able to discern the most common impurities, and therefore the most common synthesis methods of MDMA, in the samples seized at the French border for the previous year (22).

A study examined the analysis of ecstasy seized in Hong Kong by GCMS. The study found GCMS to be a useful and accurate method of identifying the impurity compounds within samples of ecstasy, and also concluded that the information gathered would be a helpful addition to information gathered by intelligence agencies when understanding the drug underworld (23).

Another example of the uses of GCMS is a study done in 2010 using the authentic references from the US special testing and research laboratory. They posed the question of whether GCMS analysis was capable of distinguishing heroin samples based on geographical origin. In this study the acidic and neutral impurities that arose during manufacture were compared using qualitative and semi-quantitative data analysis. Impurities that are unique to a particular geographical source were found and samples were able to be discriminated based on those. Although there were some highly refined samples from South America and South-West Asia that were indistinguishable from each other due to lack of presence of impurities. This shows that this method of analysis is a good way to discriminate samples based on source location however is limited by the amount of impurities in a sample (24).

GCMS is an incredibly useful technique for the impurity analysis of illicit substances. It allows for the identification of impurities due to its ability to separate them out through the chromatography and acquire information on individual chemical characteristics through the mass spectrum. However, its separation is not perfect and sometime fails to separate similar compounds, and it requires more sample preparation and longer analysis time.

1.5.3 Nuclear Magnetic Resonance

Along with GCMS a standard method of analysis is nuclear magnetic resonance spectroscopy (NMR). This technique is helpful in that, because it measures the difference in environments of the atoms present, it allows the differentiation between isomers that would otherwise have the same mass spectrum. This technique has the ability to focus on many different atom environments, the most common of which use hydrogen and carbon 13. There are also 2D versions of the analysis which will be discussed shortly. Through this technique identification of at least the main constituent of a sample is achievable in great detail. However, unless there are obvious major and minor components in a sample, determining which signals belong to which compounds can be incredibly difficult.

A study performed in 2013, examined the use of NMR Spectroscopy in identifying the impurities of cocaine samples seized in Italy. Samples were analysed by NMR and then GCMS as a confirmatory method. By analysing the peaks in the NMR spectrum, they were able to identify, first the peaks pertaining to the actual cocaine, then identity of the cutting agents used in the different samples, then the identity of the minor components within the drug sample. They concluded that this information can be helpful to police by confirming links already made by circumstantial evidence, but also to suggest new links that can be investigated. They also suggested that the ratios of the minor components in the cocaine samples could be used to determine the geographical origin of the plants used to manufacture the cocaine (25).

Another study was done in 2014 that looked at ^{1}H NMR and two-dimensional diffused-ordered spectroscopy (2D DOSY) ^{1}H NMR in the context of heroin profiling (26). In the study, heroin, its cutting agents, and its impurities were all analysed using this method. A majority of the compounds in the heroin samples were able to be identified, 2D DOSY ^{1}H NMR was particularly helpful for identifying compounds that were unable to be identified in the standard 1D ^{1}H NMR due to peaks overlapping. This technique was

found to be suitable for analysing the major components of the heroin sample including heroin itself, cutting agents, and major impurities. However some minor impurities with similar diffusion coefficients are difficult to separate from one another even with 2D DOSY ^{1}H NMR (26).

As problematic as this overlapping of signals seems, this technique is extremely compatible with GCMS and enables extra information to be obtained that is otherwise out of reach using either analytical technique alone. A study published in 2015 on the organic impurity profiling of MDMA, was only able to come to a particular conclusion about the identity of an impurity because of both NMR and GCMS used together. The compound shown in Figure 9 below was found to be an impurity in MDMA, the mass spectrum of which was found to have an abundance of the methylenedioxytoluene structure, however there was nothing more that indicated the complete structure. The NMR was then shown to contain an extra peak that is characteristic of a pair of hydrogens not surrounded by any electronegative atoms or any other hydrogens. This allowed the structure shown in Figure 9 to be determined which was not possible when using only one of these methods in isolation (27).

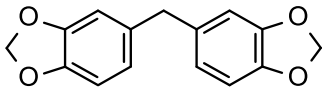


Figure 9: An impurity found in MDMA synthesised from catechol by Heather, Shimmon, and McDonagh 2015.

Its use, therefore, in the organic impurity profiling of illicit drugs is partial. It creates a unique “fingerprint” of the drug sample and its impurities which can be used to compare samples and establish links. However, it is not the most useful technique available with regard to identifying the organic impurities that create a particular “fingerprint” although is useful when used in conjunction with other techniques.

1.6 Additional Techniques

1.6.1 Raman Spectroscopy

Raman spectroscopy is a technique that takes advantage of the unique way a substance scatters energy based on the change of polarizability of a molecule, creating a specific spectrum through which identification of a substance is possible (28). Much like FTIR, this technique requires little to no sample preparation and the data is acquired very quickly

in only a matter of seconds. However, also like FTIR, Raman lacks the ability to separate out complex mixtures and therefore it is unable to effectively identify the minor components of a sample (28), a prized ability in organic profiling. However, this technique is still highly useful in the comparison and linking of street drug samples for intelligence.

Bell et al looked at the benefits of using Raman spectroscopy for discriminating ecstasy tablets of similar appearance seized in the UK based on cutting agent and the ratio of cutting agent to drug. The study concluded that Raman is a useful method for further analysis and grouping of those tablets that were already grouped according to appearance. They were able to group the similar looking tablets according to cutting agent, and within those groups were able to further group the tablets based on the percentage of the tablet that is the active ingredient. But the main conclusion drawn from this research is that it is really helpful technique to police due to the very fast run times of each sample, with 50 samples able to be analysed in one hour. Being able to run more samples in the same amount of time enables analysts to overcome sampling errors that can arise from sample size limitations caused by time restraints (29). However, it is not able to be used for minor component/impurity identification. Similar to the FTIR the resulting spectrum is based on types of bonds, and therefore a mixture is extremely difficult and near impossible to interpret in any meaningful way when trying to identify the constituents of the tablet (29).

1.6.2 2D- Gas Chromatography

Two-dimensional gas chromatography (2D-GC) works much like the gas chromatography except when the sample leaves the column, instead of being detected and then entering a mass spectrometer, the sample is passed through another GC column and separated further (30). Therefore, a single GC peak, where similar compounds would normally fail to be resolved, is able to be separated out and the individual compounds are able to be identified. This is helpful when dealing with a number of different, very similar compounds, which is what impurities in drugs normally are. A study performed in Germany looked at the application of 2D-GC in the profiling of seized cannabis and heroin samples; which then paired this with a pixel-based hierarchical analysis method. From this research it was found that in general the results obtained about groupings of the drugs were in accordance with the result generated by the approved methods. The discrepancies are probably due to the small sample size worked with. The samples were able to be grouped and the minor components of the samples identified, the information

that is collected from this analysis method is very useful within the greater community of illicit drug analysis and investigation (31).

1.6.3 Isotope Ratio Mass Spectrometry

Isotope ratio analysis measures the ratio of abundance between the common weight for an atom and its isotope. It is a form of mass spectrometry and therefore measures the weights of the differing isotopes in the same way that the compound fragments that make up a regular mass spectrum are measured (32). Because different reactions can favour different isotopes of the atoms, the isotope ratio of an illicit drug sample can be used to differentiate the samples according to synthesis method. Salouros et. al 2013 investigated whether methamphetamine samples could be distinguished according to synthesis method by only the sample's isotopic ratio alone. The study included the analysis of $\delta^{15}N$, $\delta^{13}C$, and $\delta^{2}H$ by an elemental Analyzer/Thermal Conversion-Isotope Ratio Mass Spectrometer. Through k-means clustering analysis they found distinct differences between the MA synthesized using natural, semi-synthetic, and fully-synthetic starting materials. That is, that the source of the ephedrine/pseudoephedrine used was extracted from the ephedra plant, synthesized via the fermentation of sugars, or made from the synthetic propiophenone (33). This type of analysis is useful when dealing with purified samples because it identifies characteristic difference within the desired compound itself. Well purified samples, even down to the level of amphetamine isomer, are becoming more and more common so having an analysis method that doesn't rely on the presence of impurities is advantageous. This study shows that even without the presence of route specific impurities the synthetic route used can still be determined and that intelligence can them be utilised by law enforcement.

1.7 Impurities

The profile of the chemical impurities is an important aspect of illicit drug profiling. There are several types of impurities that can be found when analysing a drug in this context. The parts that make up a drug profile are, the illicit drug compound itself and cutting agents, then the types of impurities which are contaminants, by-products, and intermediates of the synthesis (Figure 10). The most significant type of compounds encountered in street drug samples, other than the drug itself, are 'cutting agents', these are essentially fillers, inert compounds that are used to dilute the concentration of the drug before it is then sold to the user. The other types of impurities occur before the drug is diluted, they arise within the synthesis of the desired drug, of which there are a few

different types of impurities. There are 'intermediates', these are compounds that arise in a multi-step synthesis method where the precursor is converted into this compound to then be able to be converted into the final product. However, since synthesis routes often have more than one step there will be multiple different intermediates. The precursor itself is also often found as an impurity in the final product but for the purposes of this study it comes under the category of intermediate. There are 'by-products' that are compounds formed from side reactions within the main reaction, for example: intermediates reacting with one another. The word 'contaminants' will be used to describe compounds that arise from the already present impurities in the starting materials and any compounds that are formed from reactions between intended compounds and these compounds throughout the reaction. 'Impurities' will be used generally to cover all these subclasses (34).

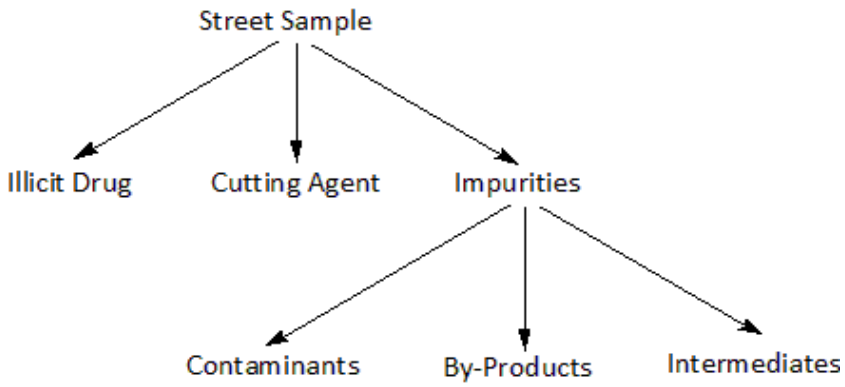


Figure 10: The components of a 'typical' illicit drug sample

The profiles showing all these impurities contain information that can be translated into intelligence for the police and law enforcement agencies to use. The profile of the seized drug can be compared to other profiles in the database to potentially link cases, or find out the geographical origins of the drug (35). In 2003, Cheng, Poon and Chan looked at the profiles of MDMA tablets seized in Hong Kong and found that a significant number of tablets were a combination of MDMA and other substances, such as; MA and ketamine. The ratio between the active drugs in the mixture was then used to create links between samples (36). Alternatively, the impurity profiles of minor components can be examined and the starting material used and the route of synthesis can be determined. Within the synthesis of the drug there are impurities that arise regardless of how well the synthesis is done. Within these impurities there are some that have only been found in products that have come from a particular starting material using a particular method. A Polish study published in 2005 looked at five different impurity profiles of MDMA, each

made by a different method of synthesis and found a few different compounds that were unique to a particular synthesis method (37). Figure 11 represents the impurities found after each method, which ones are common to multiple methods, and which ones are unique to a specific method of synthesis.

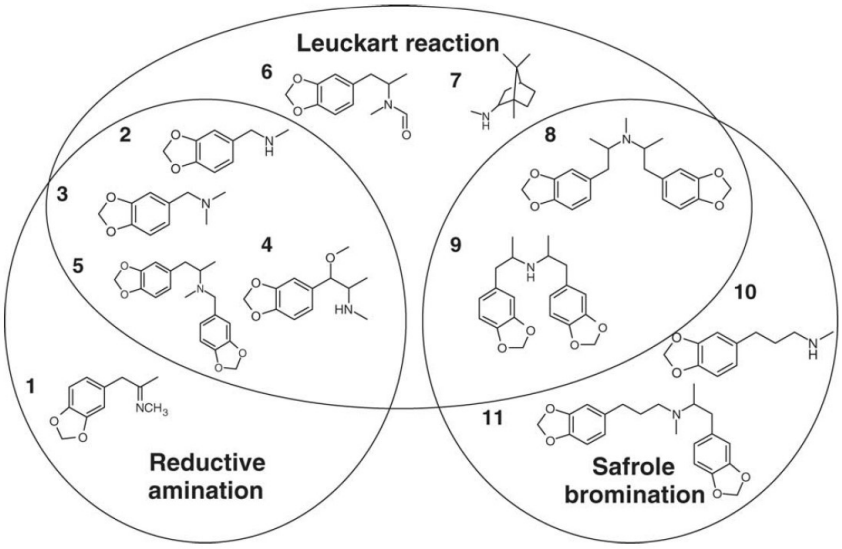


Figure 11: The findings by Swist, Wilamowski and Parczewski in 2005 in regards to the impurities found in MDMA made by 3 different synthesis methods (37)

Multiple studies have been done on connection between specific organic impurities of amphetamines and synthesis routes, each concluded that this information is a helpful addition to physical characteristics when determining the origin of ecstasy tablets, especially when the identity of the impurities found with respect to each synthesis method have been consistent across the studies (38, 39). Another similar study looked at the impurity profiles of 4-methoxymethamphetamine (PMMA) made by two different synthesis methods and found compounds that are unique to each, although, this research suggested more study into other synthesis routes and their profiles in order to increase discriminating power (40).

1.8 Profiling of other Illicit Substances

As previously demonstrated, there are a number of different illicit drugs that have been chemically profiled, and this information has been useful within the law enforcement agencies, but really only in the analysis of ATS are the impurities used to infer the synthesis route and the starting material. The impurity profiles of heroin and other semi-synthetic drugs can be used to match other samples from particular batches and infer a particular origin, but not much information can be gained from only one profile. In

contrast to semi-synthetic drugs like heroin, which have a very limited number of synthesis routes, fully-synthetic drugs like ATS can be made in multiple different ways from a wide variety of starting materials. Therefore, figuring out the synthesis route and starting material of an ATS is more helpful to police investigation and has a higher discriminating power than would otherwise be with other drugs.

In 2013 a review was performed of some common ATS and their most well-known and used synthesis methods and starting materials. This review reinforces the variety of options available when it comes to producing ATS and the enormity of the task law enforcement and researchers have in studying them. The review looked at methamphetamine (MA), MDMA, amphetamine (AP), dimethylamphetamine (DMA), and p-methoxyamphetamine (PMA) and the impurities that occur during their synthesis processes. Figure 12 shows MA made from ephedrine, pseudoephedrine, or P2P and the multiple relevant synthesis methods. Figure 13 shows the synthesis methods of MDMA from safrole, isosafrole, and piperonal. Figure 14 shows the synthetic routes to create AP from norephedrine, norpseudoephedrine, benzaldehyde, and P2P. It looked at the synthesis of DMA from methylephedrine or methylpseudoephedrine using the methods shown in Figure 15. Lastly, it looked at the synthesis methods for PMA from anethole and PMP-2-P shown in Figure 16. The review summarised all the available data generated by other external studies on the specific impurities found in each type of amphetamine made from each of the relevant syntheses. The compounds concluded to be route specific were then compared across other studies in order to confirm the validity of the conclusions (34).

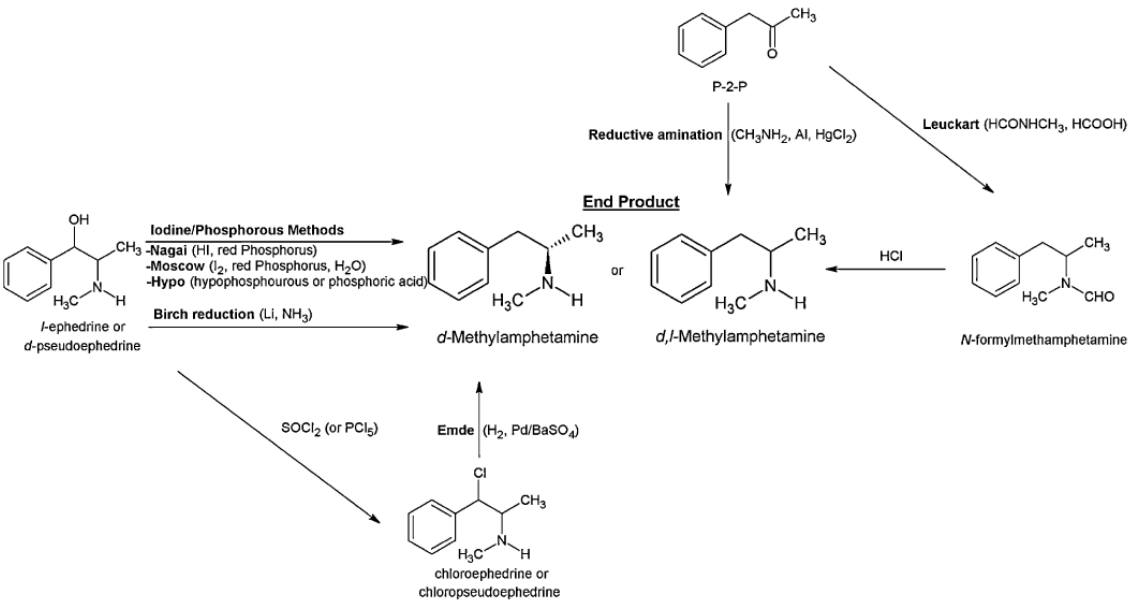


Figure 12: Synthesis methods for MA (34)

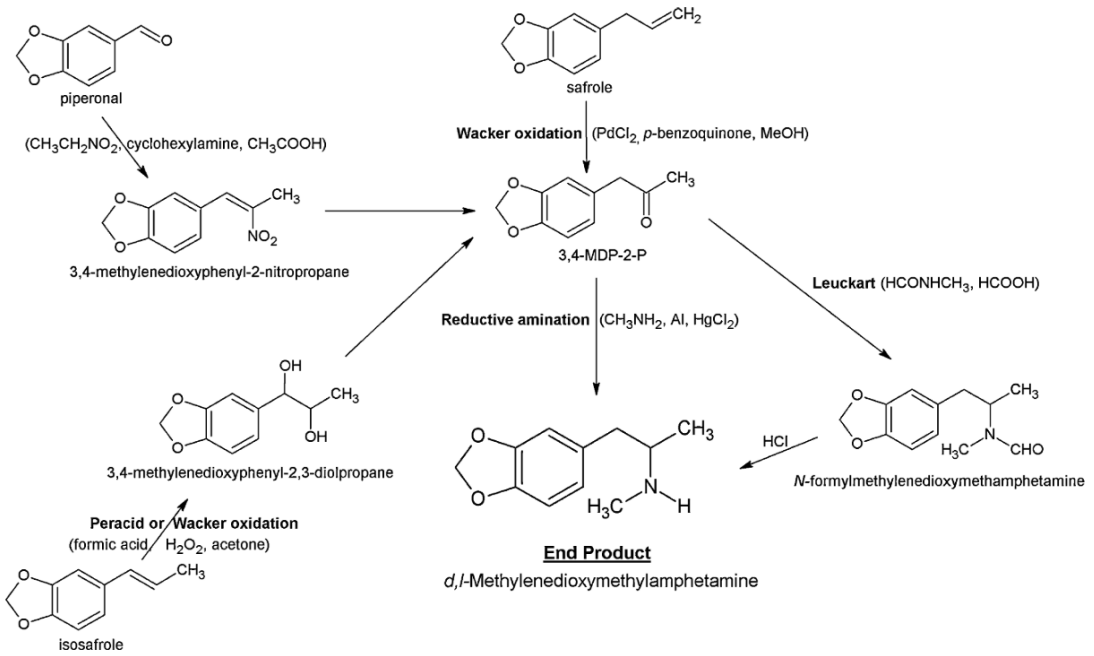


Figure 13: Synthesis methods for MDMA (34)

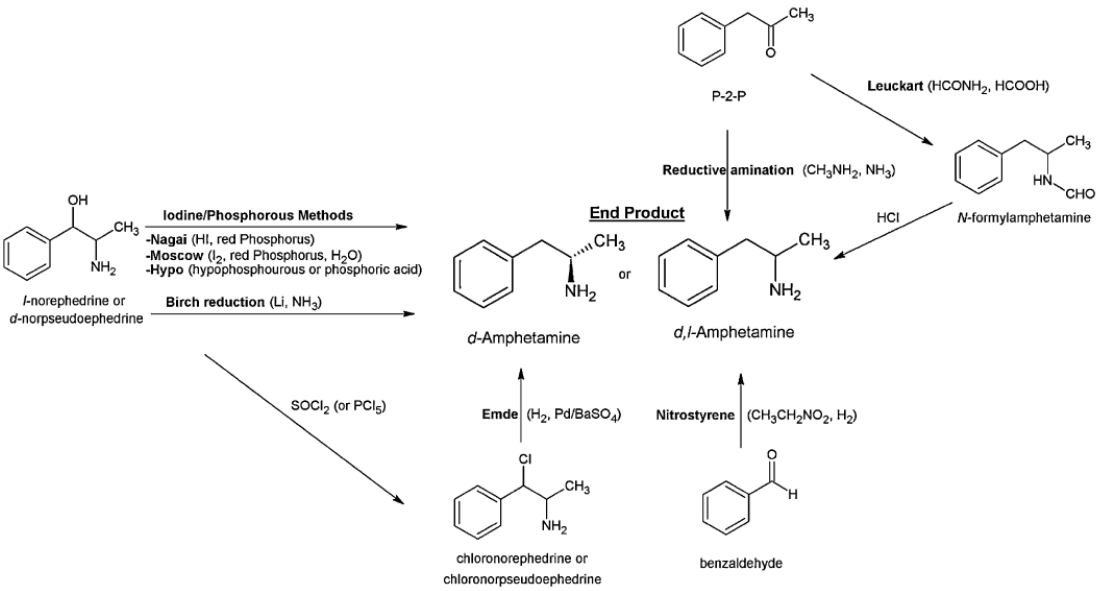


Figure 14: Synthesis methods of AP (34)

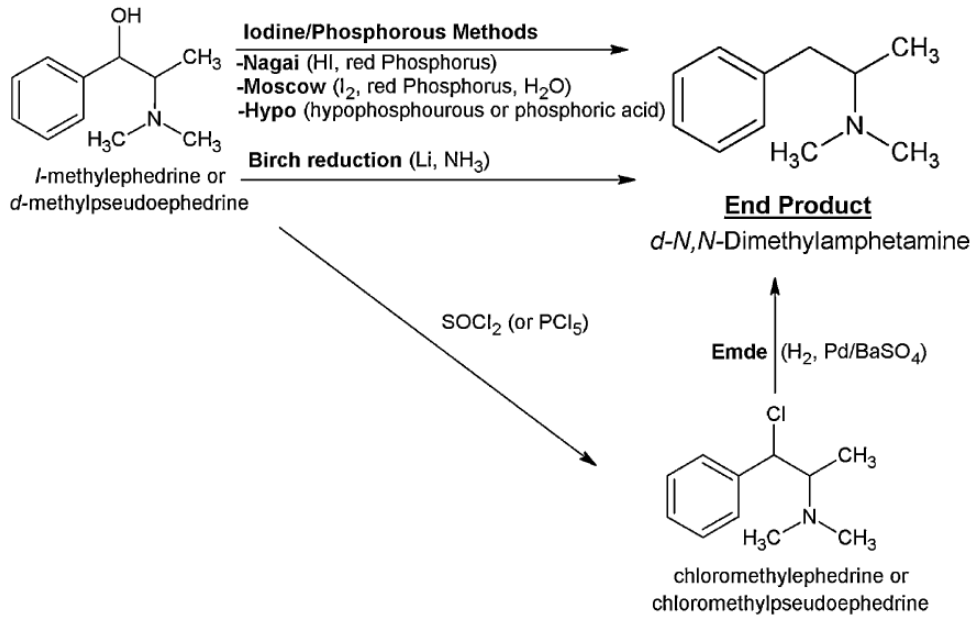


Figure 15: Synthesis methods for DMA (34)

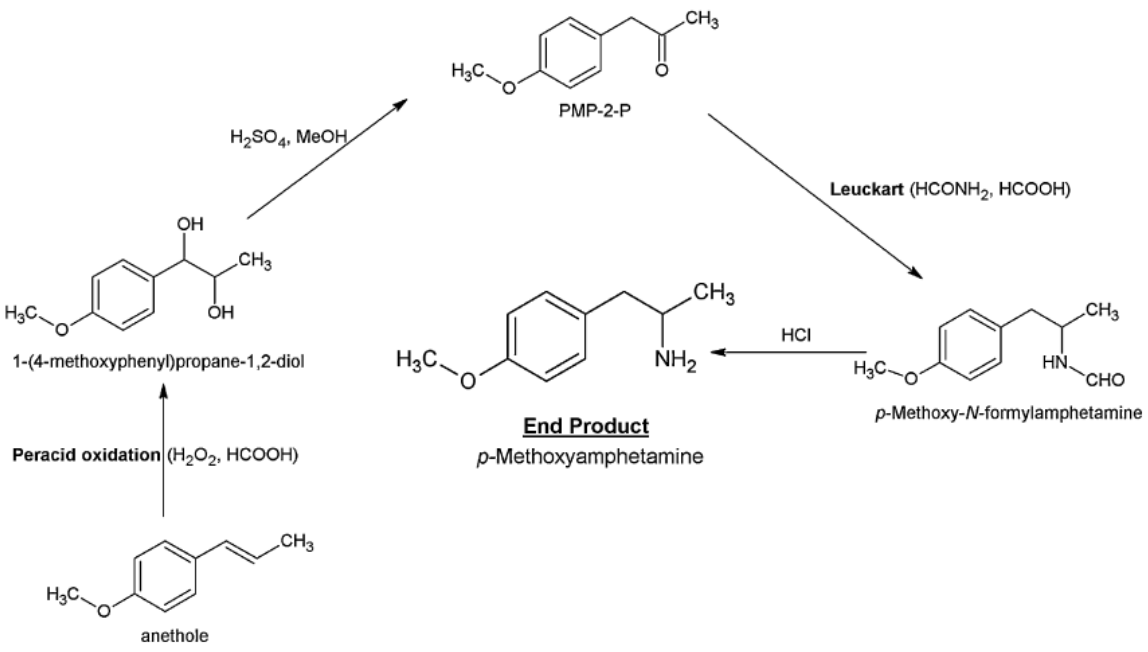


Figure 16: Synthesis method for PMA (34)

In this review only the impurities concluded to be route specific by each of the external studies were discussed and compared. Below, in table 1, is a summary of all the impurities discussed and concluded to be route specific in this review. It shows the route specific impurities first according to final product, then according to the synthesis method used to make that final product (34).

Table 1: Route specific impurities discussed in Stojanovska et al. 2013 organised according to final product compound and synthesis method.

Compound	Method	Route Specific Impurities
MA	Reductive Amination	1-Phenyl-2-propanol, amphetamine, 1,3-diphenyl-2-methylaminopropane, N-cyanomethyl-N-methyl-1-phenyl-2-propylamine
	Nagai	(2E)-N-Methyl-3-phenyl-N-(1-phenylpropan-2-yl)prop-2-enamide (cis-cinnamoyl derivative of MA), iodoephedrine, N-methyl-N-(a-methylphenyl)amino-1-phenyl-2-propanone, (Z)-N-methyl-N-(a-methylphenylethyl)-3-phenylpropanamide
	Emde	Chloroephedrine/chloropseudoephedrine, methylephedrine, N-formylephedrine, N-acetylephedrine, N,O-diacetylephedrine, N-acetylamphetamine
	Birch	1-(1,4-Cyclohexadienyl)-2-methylaminopropane
	Leuckart	a-Benzyl-N-methylphenethylamine, a,a'-dimethyldiphenethylamine, N-a,a'-trimethyldiphenylamine
MDMA	Reductive amination	3,4-Methylenedioxy-N-methylbenzylamine, 4-methyl-5-(3,4-methylenedioxyphenyl)-[1,3]-dioxolan-2-one, N-methyl-2-methoxy-1-methyl-2-(3,4-methylenedioxyphenyl)-ethanamine, N-cyclohexylacetamine, 1,2-methylenedioxy-4-(2-N-methyliminopropyl)benzene, N-cyanomethyl-N-methyl-1-(3,4-methylenedioxyphenyl)-2-propylamine, N,N-di-[1-(3,4-methylenedioxy)phenyl-2-propyl]methylamine (MDMA dimer)
	Leuckart	p-Bromotoluene, N-ethylamphetamine, N-ethylmethamphetamine, N-formylamphetamine, N-formyl-MDMA, 5-(1,3-benzodioxol-5-ylmethyl)pyrimidine, 3,4-bis-(1,3-benzodioxol-5-ylmethyl)pyridine
	Wacker oxidation	1-(3,4-Methylenedioxyphenyl)-1-methoxypropan-2-one, methyl-3-(3,4-ethylenedioxyphenyl)-propanoate, 1-(3,4-methylenedioxyphenyl)-1,3-dimethoxypropane, 3-(3,4-ethylenedioxyphenyl)-1,1-dimethoxypropane, 1-(3,4-methylenedioxyphenyl)-1-methoxypropane
	Peracid oxidation	2,4-Dimethyl-3,4-bis(3,4-methylenedioxyphenyl)tetrahydrofuran, 1-(3,4-dimethoxyphenyl)-2-propanone, 1-(3,4-methylenedioxyphenyl)-1-propanone, 2,2,4-trimethyl-5-(3,4-methylenedioxyphenyl)-[1,3]-dioxolane, 1-(3,4-methylenedioxyphenyl)-1,2-propanedione, 1-methoxy-1-(3,4-methylenedioxyphenyl)-2-propanol
AP	Emde	Chloronorpseudoephedrine/chloronorephedrine
	Birch	1-(1,4-Cyclohexadienyl)-aminopropane
	Leuckart	a-Benzylphenylethylamineformamide, 4-benzylpyrimidine, 4-methyl-5-phenyl-pyrimidine, 2,4-dimethyl-3,5-diphenylpyridine, 2,6-dimethyl-3,5-diphenylpyridine
DMA	Nitrostyrene	(2-Nitroprop-1-enyl)benzene, benzyl methyl ketoxime, N-(b-phenylisopropyl)benzaldime
	Nagai	1-Propenylbenzene, 2-propenylbenzene
	Emde	Chloromethylephedrine/chloromethylpseudoephedrine, 1-dimethylamino-1-phenyl-2-chloropropane
	Birch	1-(1,4-Cyclohexadienyl)-2,2-dimethylaminopropane
PMA	Leuckart	4-(4-Methoxybenzyl)pyrimidine,4-methyl-5-(4-methoxyphenyl)pyrimidine, 2,4-dimethyl-3,5-di-(4-methoxyphenyl)pyridine, 2,6-dimethyl-3,4-di-(4-methoxyphenyl)pyridine
	Peracid oxidation	4-Methoxyphenol

3,4-methlenedioxymethamphetamine (MDMA) is the ATS most commonly profiled (27, 36, 39, 41-47) with the specific impurities identified and analysed from a large range of

starting materials and methods. One of the first studies performed on MDMA impurities in 1993, looks at MDMA made from 3 different synthesis routes, from safrole, isosafrole via N-formylMDA, and isosafrole via N-formylMDMA. They analysed the final products using High Performance Liquid Chromatography (HPLC), GCMS, ^{13}C NMR, and ultraviolet spectroscopy. Using these techniques they were able to identify the minor components and impurities within the samples of MDMA. They compared the impurities found in each route and were able to identify ones unique to a particular route. They found that if isosafrole glycol, PMK, N-formylMDMA, and DMMDA were all present then that indicated that the MDMA was synthesized from isosafrole via N-formylMDMA (46).

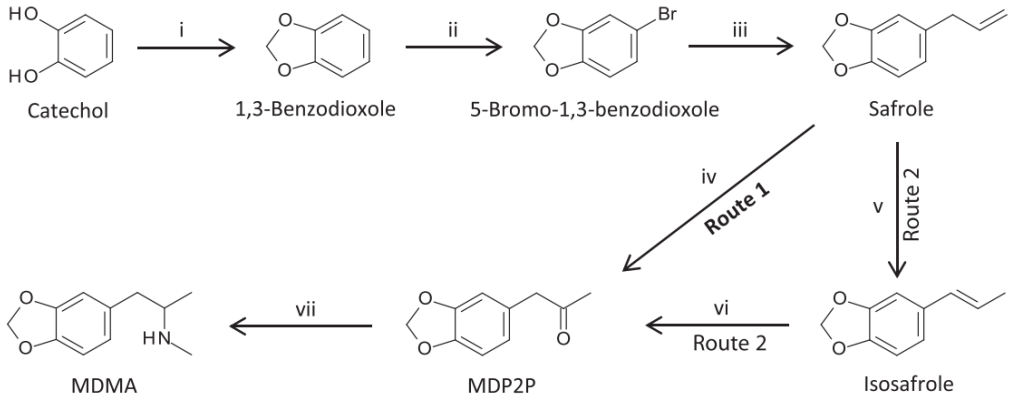


Figure 17: 2 Synthesis routes of MDMA from catechol (27).

Another more recent study that has been done is on the route specific impurities of MDMA synthesised from catechol in 2015. This study looked at the impurity profiles of the two synthesis routes shown in Figure 17 to determine if the two products could be discriminated according to synthesis route. First all the impurities were analysed to determine compounds that indicate catechol as the starting material regardless of the synthesis route, these were found to be compounds 2-6,8, and 15 in the original article and can be found in Figure 18. The impurities of each synthesis route were then compared and compounds 11, 12, and 14 of the original article were found to be unique to Route 1 as they're characteristic of MDMA from safrole via Wacker oxidation using methanol as the solvent. Compounds 18 and 19 were found to be characteristic of Route 2 (27).

As useful as these summaries are, they are not and never will be complete. Even in the years since these publications new synthetic routes have been discovered and more will continue to be discovered as clandestine chemists adapt around laws and intelligence that might lead to their detection. As they adapt so must the research which must continually

be updated to reflect the changes in the drug market. And so, the body of knowledge regarding the organic profiling of synthetic routes to illicit substances must be continually added to for law enforcement agencies to remain effective.

Table 2
Organic impurities identified in MDMA synthesised from catechol via Route 1 and Route 2.

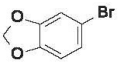
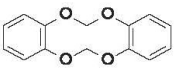
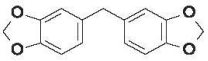
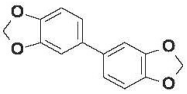
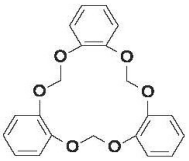
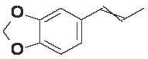
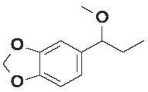
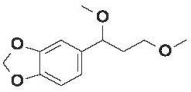
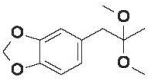
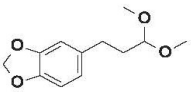
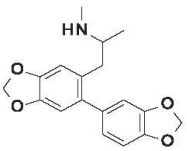
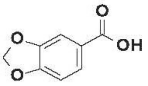
No.	Impurity structure	Impurity name	*m/z*	Synthetic route
1		1,3-Benzodioxole	122/121, 63	1
2		5-Bromo-1,3-benzodioxole	202/200, 121, 63	1 and 2
4		1,3-Benzodioxole dimer	244, 135, 122/121, 63	1 and 2
5		5,5′-Methylenebis-1,3-benzodioxole	256, 135, 77	1 and 2
6		5,5′-Bi-1,3-benzodioxole	242, 126, 121/120, 63	1 and 2
8		1,3-Benzodioxole trimer	366, 244, 135, 122/121	1
10		*cis* and *trans* isosafrole	162, 131, 104/103, 77, 44	1
11		5-(1-Methoxypropyl)-1,3-benzodioxole	194, 165, 150/149, 135, 77	1
12		5-(1,3-Dimethoxypropyl)-1,3-benzodioxole	224, 192, 161, 135, 75	1
13		MDP2P dimethyl acetal	224, 193, 135, 89	1 and 2
14		5-(3,3-Dimethoxypropyl)-1,3-benzodioxole	224, 192, 161, 135, 75	1
15		1-[6-(1,3-Benzodioxol-5-yl)-1,3-benzodioxol-5-yl]-N-methyl-propan-2-amine	256, 58, 44	1
16		1,3-Benzodioxole-5-carboxylic acid	166, 150/149, 135, 121, 77	2

Figure 18: Organic impurities identified in MDMA synthesized from catechol (27).

Table 2 (Continued)

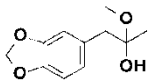
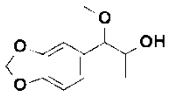
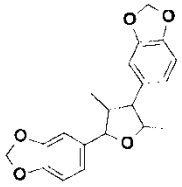
No.	Impurity structure	Impurity name	m/z	Synthetic route
17		MDP2P methyl hemiacetal	196, 165, 150/149, 135, 121, 63	2
18		1-(1,3 Benzodioxol 5 yl) 1 methoxy propan-2 ol	210, 165, 150/149, 135, 77	2
19		2,4-Dimethyl-3,5-bis(3,4-methylenedioxyphenyl) tetrahydrofuran	340, 296, 281, 207, 44	2

Figure 18 continued

1.9 MDA

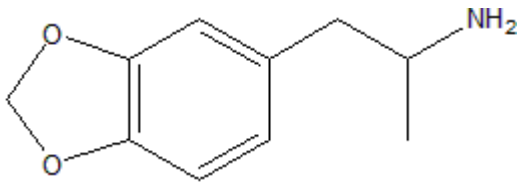


Figure 19: The specific structure of MDA

The type of ATS that will be focused on in this project is 3,4-methylenedioxyamphetamine or MDA and it's structure is shown in Figure 19. The only difference between this and MDMA is the loss of a methyl group. It is a stimulant and a hallucinogen just like MDMA and has the same effects as described earlier in this paper. There have not been any official studies performed on the difference between the effects of MDA and other ATS such as MDMA however there seems to be a general consensus within anecdotal evidence across the internet (48). Users testify that the effects of MDA seem to last longer than those of MDMA. It is said that MDA has more of a hallucinogenic effect than MDMA and MDA has less of an entactogenic effect as it does not make people feel or want to feel as connected with other people as much as MDMA does, but that's not to say that this effect isn't present.

1.9.1 Synthesis Routes

The most well-known synthesis methods for MDA involve the use of safrole or piperonal as the starting material. These methods have been documented and profiled and will be discussed in the following paragraphs. Figure 20 shows the synthesis methods of MDA from safrole and piperonal but also from helional, a method of concern for law

enforcement agencies. Another known, although rare, method of synthesizing MDA is from α-methyl-3,4-methylenediozycinnamic acid also shown in Figure 20.

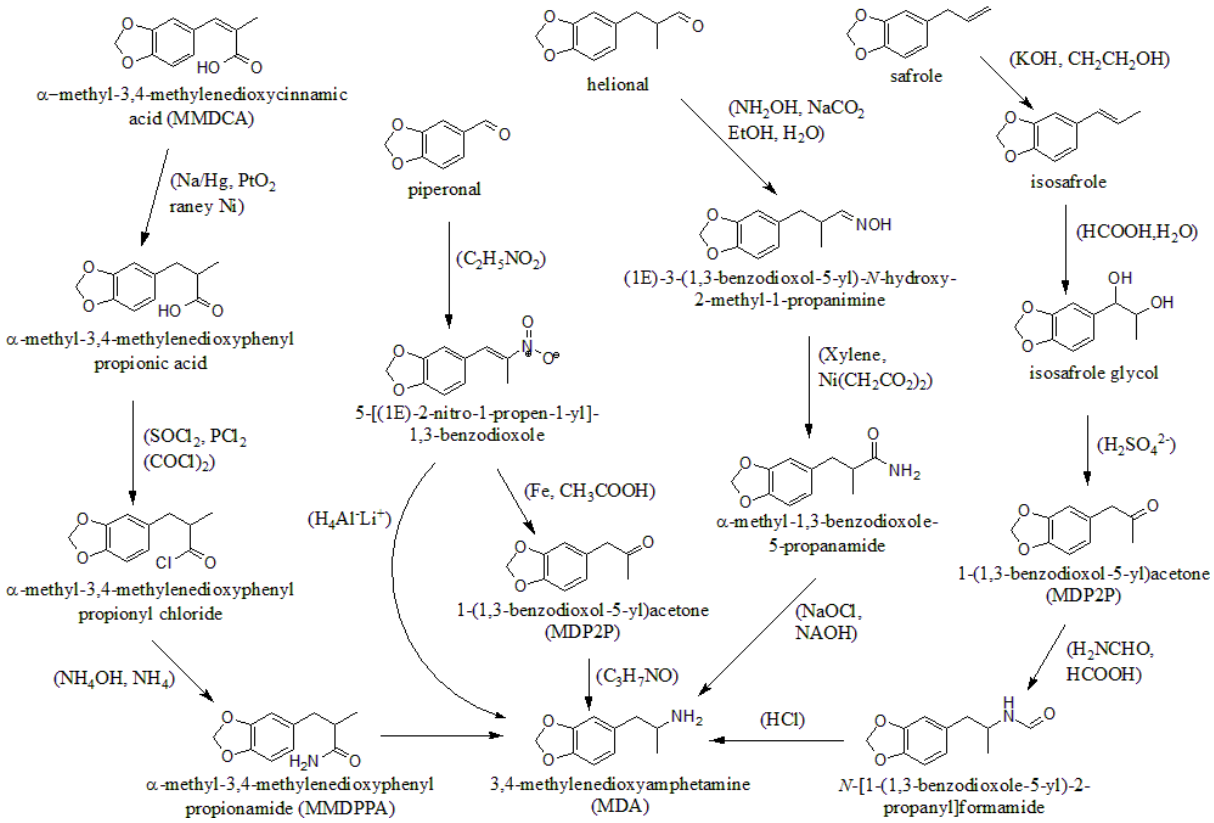


Figure 20: Synthesis routes for MDA

1.9.2 Profiling of MDA

There has been limited research into MDA and its impurity profile. A study performed in 1978 looked at the impurities in MDA made from safrole, isosafrole, and piperonal via various reactions. They identified through the analysis of samples by IR, UV, GC, MS, and NMR the identity of the impurities. It was found that the presence of the amines di[1-(3,4-methylenedioxyphenyl)-2-propyl]amine and di[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine indicated the use of the Leuckart reaction from safrole as the starting material. They also found that the presence of 1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene can indicate the synthesis of MDA from piperonal (49).

Another study that had an in-depth look at the impurities of MDA depending on synthesis route was Bohn, Bohn, and Blaschke in 1993 (42). This study looked at the impurities in MDA made from isosafrole by the Leuckart-Wallach method and found compounds VI-XI in Figure 21, were unique to the Leuckart-Wallach reaction. Compound XV was also suggested to be unique to this synthesis route. These results agree with the previous study

by Lukaszewski. MDA made using reductive amination was also examined and found that the presence of compound XI could potentially indicate this synthesis pathway (42).

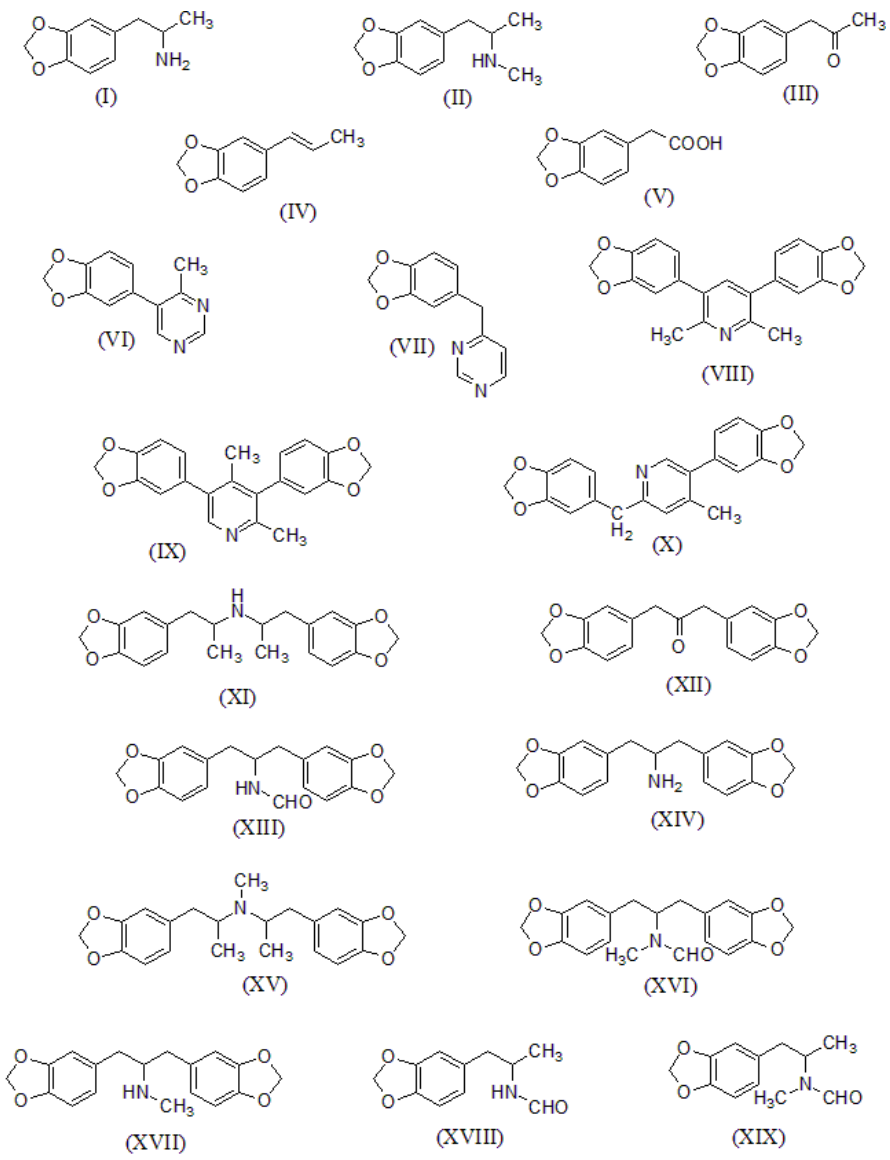


Figure 21: Impurities of MDA made from 3 different methods (42)

The common routes for synthesis of MDA are those from piperonal, safrole, and isosafrole all of which are controlled substances under the following international and Australian legislation: United Nations: Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances 1988 (50), Criminal Code Regulations 2002 (Australia) (51), Drugs Misuse and Trafficking Act 1985 (NSW) and Drug Misuse and Trafficking Regulation 2011 (NSW) (52). All other Australian states have legislation restricting these substances (53-58). MDMA synthesis methods and their subsequent route specific impurities have been thoroughly profiled by a variety of methods (16, 27,

34). While there is literature available on MDA synthesis there is not the same plethora of studies and published articles on the subject. The information generated in this proposed study is useful to the greater society in its application to police intelligence. Through information about synthesis route and any possible linked samples law enforcement is able to better go about investigations into the illicit drug market, specifically that of MDA. They are able to get a more accurate understanding of trafficking routes and target correct and more foundational suppliers.

1.10 Aims and Objectives

The aims of the project that follows this paper are:

1. Synthesize MDA from helional and piperonal.
2. Identify the impurities that arise at each step of both syntheses.
3. Identify route-specific impurities that indicate MDA production from helional.

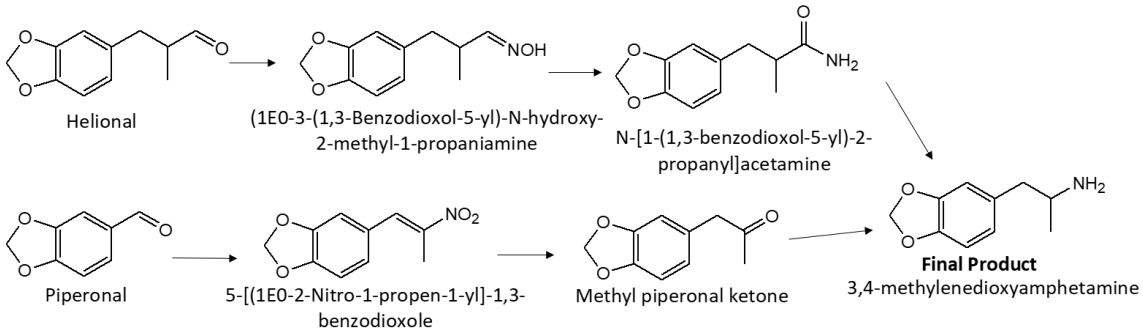


Figure 22: Synthesis of MDA from helional and piperonal

A priority area that has been identified by the New South Wales Police is the synthesis of MDA from helional. Helional is not a compound under any legal restrictions within Australia. It is a compound common in many fragrances and is therefore available for wholesale both commercially and to home perfume makers. Because of this it's relatively cheap to obtain compared to other known and restricted starting materials for MDA. Its chemical structure is visibly similar, already containing the necessary 3,4-methylenedioxy ring and a carbon chain with convenient branching, this means the synthesis is simpler than would otherwise be. A synthesis of MDA from helional has been published online under the name "2 dogz method" which involves the synthesis outlined by the top row of Figure 22. Currently there are no studies done identifying the by-products from this method of synthesis or investigation into whether there are any route specific by-products. This synthesis method will be replicated in our laboratory and

investigated for organic impurities. The results found will be compared to the results from previous studies profiling the impurities of MDA synthesised using other methods to determine if any are route specific impurities. The synthesis method being followed in this study is outlined in Figure 22. This study will fulfil the role for MDA that the numerous studies of the profiling of MDMA played in providing additional intelligence that impacted the supply chain for MDMA.

The analysis methods that will be used in order to identify the impurities within the substance will be the FTIR, GCMS, and ^{1}H NMR which have been discussed previously. FTIR will be used as a preliminary measure to assure that the reaction has worked. GCMS will be the primary analysis method for identifying the individual compounds as it has the power separate them out from one another. ^{1}H NMR will be used as a confirmatory analysis for ensuring the correct product is made and the correct isomer of that product.

As well as theoretical comparison of results across previous studies, there will be actual comparison of different methods within this study. Another synthesis that will be undertaken for the purpose of impurity comparison will be MDA made from piperonal. This is a well-known method which therefore provides a good basis for comparison where the number of variables at work is at its minimum. The process by which MDA is synthesised from piperonal is also outlined in Figure 22.

2. Materials and Methods

2.1 Instrumentation

GCMS experiments were performed using an Agilent 6890 Series Gas Chromatographic System coupled to an Agilent 5973 Network Mass Selective Detector. Samples were prepared at concentrations of 5-10 mg/mL in an ethanol solution. The column was a Zebron ZB-5ms 5% polysilarylene-95% (5%-phenyl-95%-dimethylpolysiloxane) with a length of 30 m, diameter of 0.25 mm and a film thickness of 0.25 mm. The front inlet was at a temperature of 250°C and had a split injection, with a 1.0 µL injection volume and a 25:1 split ratio. The transfer line was at a temperature of 280°C. Helium was used as a carrier gas at a rate of 1.2 mL/min. The temperature programme had an initial oven temperature of 50°C for 2 min, followed by a ramp of 10°C/min until 290°C where it was held for 4 min. The scan parameters enabled collection of a mass range of 45–450 amu with an abundance threshold of 100. The data were analysed using MSD Chem Station software.

The NMR instrument used was an Agilent Technologies 500 MHz NMR instrument. The samples were dissolved in either deuterated chloroform or ($CDCl_3$) or D_2O depending on polarity with the use of residual chemical shifts of 7.26 ppm and 4.79 ppm (59) respectively. The ^1H NMR spectra were collected at 25°C with the following acquisition parameters: 16 acquisitions, 8012.8 Hz spectral width, 4.089 s acquisition time, 1.0 s relaxation delay and 60.0 degree pulse.

2.2 Chemicals

Sodium hypochlorite solution 12.5%, acetone, ethanol, sodium sulfate anhydrous 98%, and sodium carbonate anhydrous 98% were purchased and used as supplied from Chem-Supply. Sodium hydroxide 97%, hydroxylamine HCl 99%, 2-methyl-3-(3,4-methyl-enedioxyphenyl)-propanal 98%, diethyl ether, diethyl ether hydrochloric acid, d-chloroform, deuterium oxide, nitroethane, piperonal, ammonium acetate, glacial acetic acid, and dichloromethane were purchased and used as supplied from Sigma-Aldrich. Nickel acetate 98%, and xylene were purchased and used as supplied by Ajax Chemicals, and iron pin dust from M&B Chemicals.

2.3 Synthesis

The method for the synthesis of MDA from helional is the ‘2 dogz’ method (60). This method involves a reduction reaction, Beckmann rearrangement, and a Hoffmann

reaction to obtain the amine base product. The synthesis of MDA from piperonal is an adaptation of the method used by Tam et al (2016) to synthesize PMMA from 4-methoxyphenyl-2nitropropene. These methods were chosen for the accessibility of the starting materials and reagents. The products of each step of both syntheses were analysed using gas chromatography coupled with mass spectrometry (GCMS) and proton nuclear magnetic resonance spectroscopy (^{1}H NMR) for impurity identification. Identification of impurities, intermediates, and products were made through a comparison to data previously published on the same compounds.

2.3.1 Synthesis of MDA HCl from Helional

Synthesis of 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime from helional

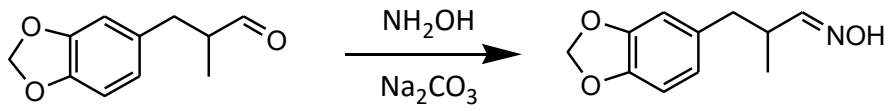


Figure 23: Synthesis of 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime from helional

Helional (1 g) was dissolved in ethanol (2 ml) in a 50 mL beaker with stirring. Hydroxylamine hydrochloride (1 ml, 50% w/v in water) was added. An aqueous solution of sodium carbonate (1 ml, 40% w/v) was added dropwise with stirring and the mixture was stirred at room temperature for 19 hours. A light brown coloured gel was formed and the solvent was evaporated by standing at room temperature for 1-2 days. The resultant aldoxime compound was used directly in the subsequent procedure without purification. m/z: 135, 189, 77, 51, 105

Synthesis of 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionamide from 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime

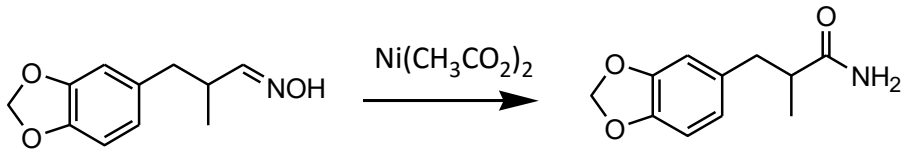


Figure 24: Synthesis of 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionamide from 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime

The aldoxime product (described above) and nickel acetate (0.02 g) were dissolved in xylene (3 ml) with stirring. The mixture was refluxed for 5 hours at 140°C in an oil bath. A dark brown solid precipitated and was collected by filtration and dried in air. M/z: 135, 207, 77, 136, 162, 105

Synthesis of MDA free base from 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionamide

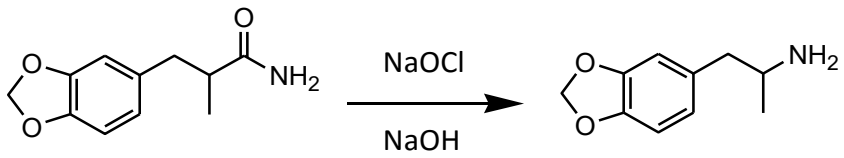


Figure 25: Synthesis of MDA from 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionamide

Sodium hypochlorite solution (1.25 ml, 4.2%) and sodium hydroxide solution (1 ml, 5%) was added to the solid amide (0.1 g). In reflux set-up the mixture was stirred, and the heat slowly increased to 80°C and held there for 30 minutes. After being allowed to cool a liquid-liquid extraction was performed with diethyl ether. Sodium sulfate was added to remove any residual water and then filtered back out. The ether solution was evaporated off leaving the amine base in the form of a dark brown oil. The method for this step was reported by Monk and Mohan 1999 (61).

MDA HCl synthesis

The amine base was dissolved into dry diethyl ether (2 ml) and HCl in diethyl ether (1 ml) was added to precipitate the amine salt. Then the solution was evaporated off. The amine salt was then washed with cold acetone and dried resulting in an off-white crystalline solid. M/z: 136, 135, 77, 51, 78

2.3.2 Synthesis of MDA HCl from Piperonal

Synthesis of 5-(2-Nitro-propenyl)-benzo[1,3]dioxole from piperonal

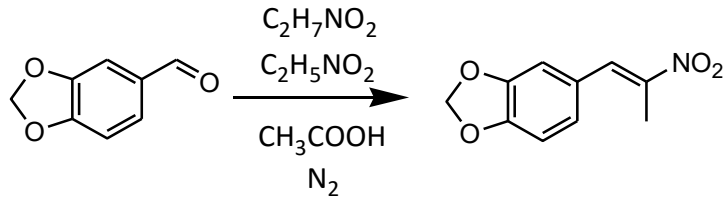


Figure 26: Synthesis of 5-(2-nitro-propenyl)-benzo[1,3]dioxole from piperonal

The method for the reaction step outlined in Figure 26 is as follows: Piperonal (1 g) and ammonium acetate (0.513 g) was dissolved into glacial acetic acid (3 ml) and stirred under nitrogen. Nitroethane (5 ml) was added and the solution stirred under reflux for 5 hours at 100°C. This resulted in a bright orange solution and the reaction was quenched with water. The solution then underwent a liquid-liquid extraction with dichloromethane, then washed with water and saturated sodium chloride solution. The dichloromethane layer

was dried with anhydrous sodium sulfate then the solution was evaporated. This resulted in a fluffy orange solid. M/z: 103, 207, 160, 77, 102. 51

Synthesis of 1-Benzo[1,3]dioxol-5-yl-propan-2-one from 5-(2-nitro-propenyl)benzo[1,3]dioxole

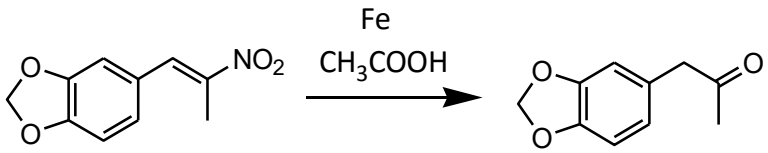


Figure 27: Synthesis of 1-Benzo[1,3]dioxol-5-yl-propan-2-one from 5-(2-nitro-propenyl)benzo[1,3]dioxole

5-(2-nitro-propenyl)-benzo[1,3]dioxole (0.1 g) was dissolved in glacial acetic acid (5 ml) then iron pin dust (0.25 g) was added to the mixture. This was stirred for 10 minutes before being heated at reflux for 2 hours at 118°C. It was then allowed to cool to room temperature before water was added and the solution was filtered to remove excess iron. A liquid-liquid extraction was done with dichloromethane then washed with saturated sodium hydrogen carbonate solution and water. The dichloromethane layer was dried with sodium sulfate and the solution evaporated resulting in a dark brown liquid (40). M/z: 135, 178, 77, 136, 51, 105

Synthesis of MDA from 1-Benzo[1,3]dioxol-5-yl-pronan-2-one

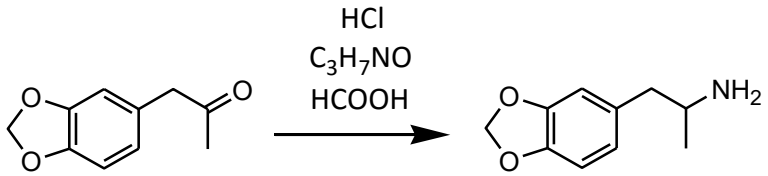


Figure 28: Synthesis of MDA from 1-Benzo[1,3]dioxol-5-yl-pronan-2-one

1-Benzo[1,3]dioxol-5-yl-propan-2-one (100mg) and ammonium formate (1g) were heated under reflux at 180°C for six hours in a sand bath. After it had cooled, concentrated HCl (3ml) was added and heated under reflux at 180°C for three hours. After it had cooled, water was added and ammonium hydroxide was added until basic. An extraction with DCM was then undertaken, the organic layer of which was dried with sodium sulfate and placed on the rotary evaporator until dry (62). The result was a dark brown solid. This product gives the same mass spectrum and ^{1}H NMR spectrum as the MDA product from helional.

3. Results

3.1 Synthetic Routes Considered

MDA was synthesized using two different starting materials, helional and piperonal. Helional is attractive to clandestine chemists as a starting material due to its legality and availability. The synthesis from helional to MDA is attractive due to its use of completely unrestricted reagents. The synthesis of MDA from piperonal was completed as a comparative measure for identifying route-specific impurities for the helional synthesis. The ability to extract piperonal from black pepper makes this synthesis comparable to the helional synthesis in terms of reagent availability and legality. An attempt was made to replicate clandestine manufacture regarding the equipment and techniques available to them. Therefore, no sophisticated purification techniques were used for products and starting materials. Impurities were analysed at each step of the synthesis and identified using GCMS and ^{1}H NMR. The helional synthesis was undertaken three times to the free base product and three times to the HCl salt. The piperonal synthesis was completed to the free base product three times.

3.2 Characterisation Procedure

The synthesis of the intended product was determined using GCMS and ^{1}H NMR. Fourier Transform Infra-Red spectroscopy was also initially used to assess whether a reaction had taken place.

The identification of unknown impurities was primarily based on the fragmentation pattern of the mass-spectra then confirmed with ^{1}H NMR where applicable. The m/z values in each mass spectrum were compared to the values for known common ions to find a base structure from which to build the unknown compound. Once that was identified the difference between the m/z peak values were calculated with these values also being compared to the values for known common ions. Then through deduction and reasoning these additional ions were added to the base structure to determine the identity of the unknown compound.

3.3 Synthesis of MDA from Helional

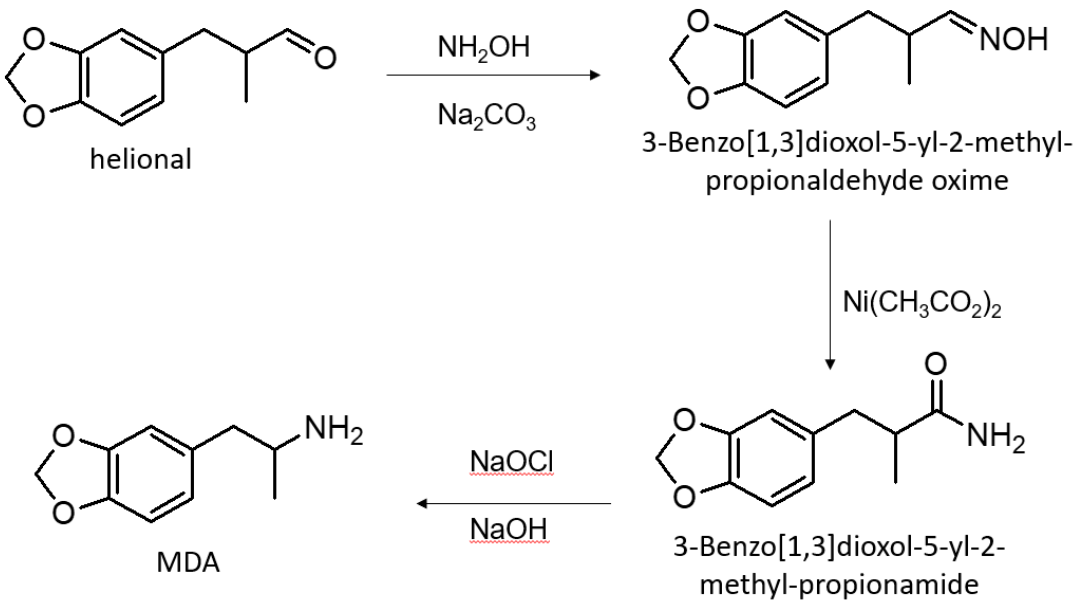


Figure 29: Synthesis route of MDA from Helional (60)

The synthesis of MDA from helional involves 3 steps as outlined in Figure 29 and will be discussed in further detail. There were no issues encountered when attempting to replicate this method and no changes were made to the method from the original plan. The synthesis of MDA from helional (the "2 dogz" method) involves three steps as shown in Figure 29. Each step is discussed in detail below together with associated ^{1}H NMR and GCMS data. For completeness, m/z data are included for peaks in the GC that could not be assigned to a reasonable structure in the current work. The GC data for each step is available in Appendix B. As well as GC and NMR data for the precursor in Appendix B and C respectively.

3.3.1 Synthesis of 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime from helional

The proposed mechanism for this step is a reduction reaction as demonstrated in Figure 30. This works through a nucleophilic attack of the partially negative free electrons on the nitrogen to the partially positive carbon in the main compound. The hydrogens on the nitrogen then reduce expelling water leaving an oxime (63).

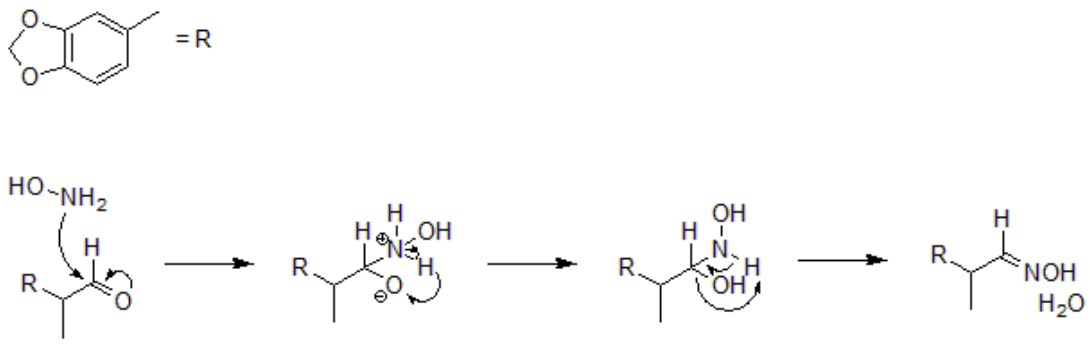


Figure 30: Mechanism of the synthesis of 3-benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime from helional

The crude product molar yield was always greater than 100% as the reaction created a lot of by-products and the product was very impure. All mentions of purity are qualitative assessment of purity as compared to a product with no impurities present and the amount of impurities present in other steps throughout the syntheses undertaken. This product was impure in that there was a large number of extraneous compounds, or impurities, detected. The consistent impurities found in the aldoxime product are summarized in Table 3 below. There were a number of other impurities present in the product than is displayed below, however their presence was only confirmed in one of the syntheses and therefore unreliable regarding their prospects as route-specific impurities. Figure 31 shows the ^{1}H NMR spectrum of the product of this step, and Table 2 shows the peak values confirming the desired product was achieved.

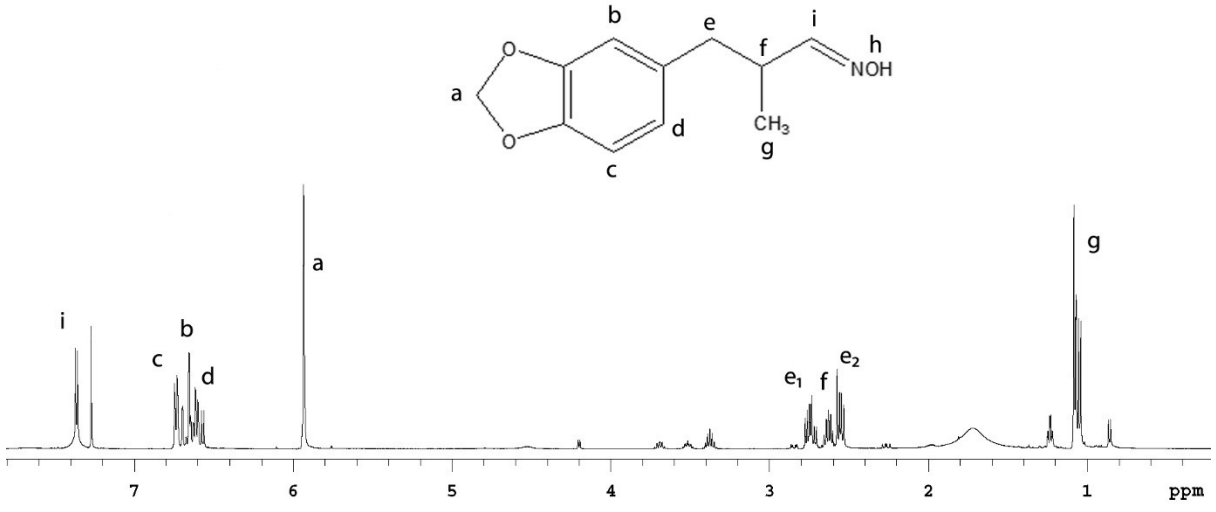
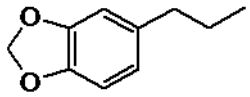
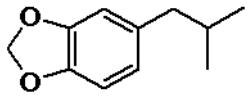
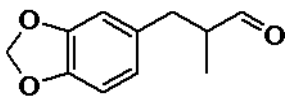
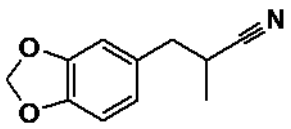
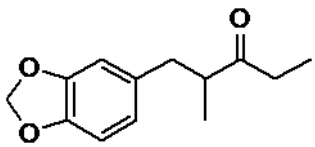


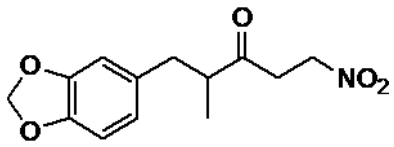
Figure 31: Annotated ^{1}H NMR for the aldoxime intermediate in the synthesis of MDA from helional.

Table 2: Chemical Shifts of peaks in aldoxime product from the synthesis of MDA from helional

Peak	Chemical Shift (δ)	Multiplicity	No. of Protons
a	5.93	Singlet	2
b	6.66	Singlet	1
c	6.75, 6.73	Doublet	1
d	6.62, 6.60	Doublet	1
e_1	2.78, 2.77, 2.75, 2.74, 2.72, 2.71	Multiplet	1
e_2	2.58, 2.56, 2.55, 2.53	Quartet	1
f	2.66, 2.64, 2.63, 2.62, 2.60	Multiplet	1
g	1.09, 1.07	Doublet	3
h	7.35, 7.36	Doublet	1

Table 3: Summary of impurities found in aldoxime intermediate of the synthesis of MDA from helional.

Compound		Name	m/z	rt	1	2	3	4	5	6
1		5-Propyl-1,3-benzodioxole	135, 164, 77, 207, 105	5.373m	X		X			
2		5-Isobutyl-1,3-benzodioxole	135, 178, 77, 164, 105	5.901m	X	X			X	
3		Helional	135, 192, 77, 136, 122, 105, 164	6.134m	X	X	X	X	X	X
4		3-(2H-1,3-Benzodioxol-5-yl)-2-methylpropio-nonitrile	135, 189, 77, 136, 105	6.296m	X	X	X	X	X	X
5		1-Benzo[1,3]dioxol-5-yl-2-methyl-pentan-3-one	135, 220, 77, 105, 189	6.358m		X	X			

6		1-Benzo[1,3]dioxol-5-yl-2-methyl-5-nitro-pentan-3-one	135, 103, 75, 220, 77, 47, 136	6.476m				X		X

The retention times (rt) in Table 3 refer to runs of 10.50 minutes. The mass spectrums of each compound can be found in Appendix C. Compounds 1 and 4 in Table 3 are consistently found in aldoximes samples. Compound 3 is the starting material helional. Compounds 1 and 2 were contaminants in the helional starting material that have carried through the reaction unchanged. Compound 4 is the intermediate of the following conversion of the oxime to the amide through a Beckmann rearrangement in the presence of nickel. Compound 4 is where that reaction stops if the reaction proceeds without the presence of nickel or another transition metal. Even though the following Beckmann rearrangement is conducted at temperatures about 140 ºC it is understood that it is only the second half of the mechanism that requires that high level of activation energy, and that a normal Beckmann rearrangement to the nitrile is conducted at the much lower temperatures of around 80 ºC (64). It would therefore be reasonable to expect, after being left at room temperature for several days, that small amounts of the oxime would have formed into the nitrile. Compound 6 is another, rarer, isomer of the aldoxime intermediate.

3.3.2 Synthesis of 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionamide (MMDPPA) from 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime

The product was mostly a dark brown solid, although for one of the repeats the solid was white. This colour difference was concluded to not be caused by a difference in organic impurities as it showed the same GCMS results and impurity profile as the other 5 samples. A potential reason for the colour difference is that the sample contained different inorganic impurities that would not be observed within the organic impurity analysis. The crude molar yield for this step is approximately 50%. This step did not have very many impurities but the ones that it did have were very consistent. This is because the preparation for this reaction step was to dissolve the aldoxime product in xylene, however very few of the aldoxime impurities were soluble in xylene and therefore did not carry through. The impurities found in the amide intermediate of MDA synthesized from helional is shown below in Table 5.

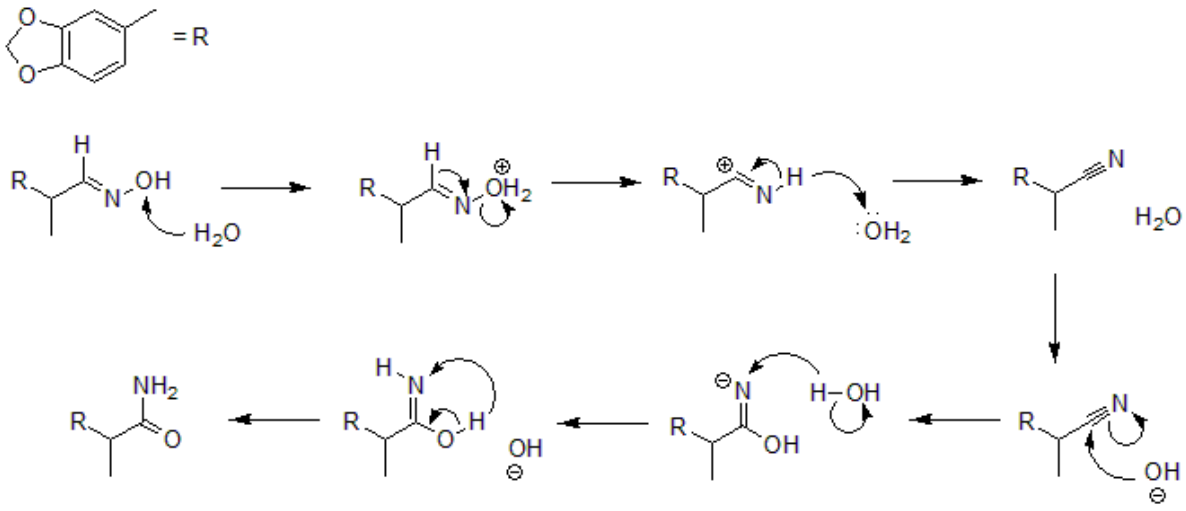


Figure 32: Mechanism of the synthesis of 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionamide (MMDPPA) from 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime

The proposed mechanism for the formation of the amide, as shown in Figure 32, is a Beckmann Rearrangement that forms a nitrile followed by a rehydration to form the amide. This process was seen by Leusink, Meerbeek, and Nolte in 1976 (64). The mechanism for the hydrolysis is outlined in the second half of Figure 32 (65). The amide product is due to the presence of the nickel salt in the reaction, without it, only the Beckmann rearrangement occurs leaving the nitrile as the main product. In the rehydration step the nitrile intermediate is a reactant but then it is reproduced as a by-product, this means that half of the oxime is turned into the nitrile and half is turned into the amide. This explains the 50% yield for the amide product. Confirmation of the production of the amide product is demonstrated in the ^{1}H NMR spectrum shown in Figure 33 with its corresponding peak values shown in Table 4. Table 5 contains a summary of the common impurities identified in the product of this step.

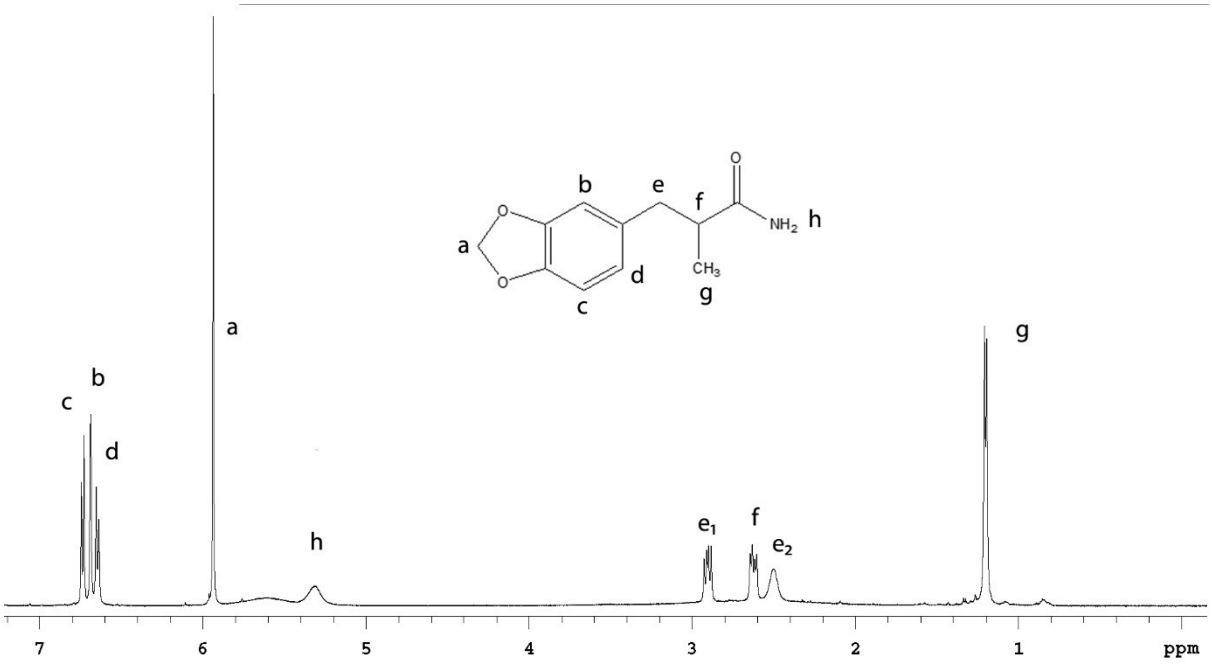
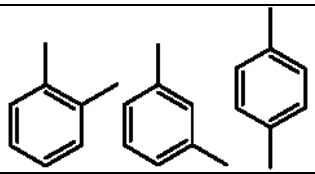
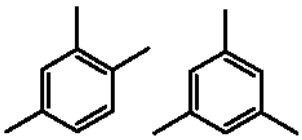
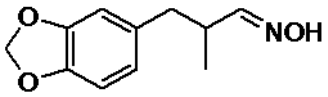
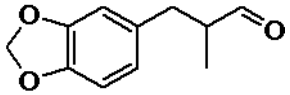
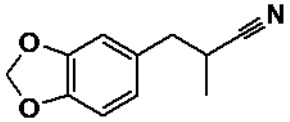


Figure 33: Annotated ^{1}H NMR of the amide intermediate in the synthesis of MDA from helional.

Table 4:Chemical Shifts of peaks in amide product from the synthesis of MDA from helional.

Peak	Chemical Shift (δ)	Multiplicity	No. of Protons
a	5.92	Singlet	2
b	6.68	Singlet	1
c	6.73, 6.72	Doublet	1
d	6.65, 6.63	Doublet	1
e_1	2.92, 2.91, 2.89, 2.88	Quartet	1
e_2	2.63, 2.61, 2.60, 2.59	Quartet	1
f	2.50, 2.48, 2.47, 2.45	Multiplet	1
g	1.19, 1.18	Doublet	3
h	5.20	Unresolved	1

Table 5: Summary of impurities found in amide intermediate of the synthesis of MDA from helional.

Compound		Name	m/z	Rt	1	2	3	4	5
1		xylene	91, 106, 40	4.229m	X	X	X	X	X
2		trimethylbenzene	105, 120, 43	4.690m		X			X
3		3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime	135, 189, 77, 51, 136, 207	6.922m	X	X	X	X	
4	UNIDENTIFIED 1		135, 220, 207, 44, 77	7.647m	X		X	X	X
5		Helional	135, 192, 44, 77, 136, 122, 105, 164	7.152m				X	
6		3-(2H-1,3-Benzodioxol-5-yl)-2-methylpropio-nonitrile	135, 189, 77, 136, 105	7.299m				X	

The retention times shown in Table 5 refer to total run times of 11.60 minutes. The mass spectrums of each impurity compound can be found in Appendix D. Compounds 1 and 2 as shown in Table 5 have been identified as xylene and trimethylbenzene respectively and are present due to incomplete drying of the solid. Xylene was the solvent used and trimethylbenzene was a contaminant in the solvent. Compound 3 is the aldoxime intermediate that remained unreacted through this step. Compound 4 remains unidentified from mass spectrum fragmentation alone. Compound 5 is helional, the starting material, and compound 6 is 3-(2H-1,3-Benzodioxol-5-yl)-2-methylpropiononitrile, this was also found as an impurity in 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime, the first intermediate product. This shows that although carry-through of these impurities is not common, it is possible. Considering that the nitrile is theoretically half of the product

of this step, it is surprising that it is only seen as an impurity once, however not so much when the method is taken into consideration. The reason why this step has so few impurities is because the amide intermediate is separated from the solution through precipitation. It could be that compound 6 fails to precipitate out of the solution, just like every other reaction product and potential impurity that may have arisen during this step of the synthesis.

3.3.3 Synthesis of MDA free base from MMDPPA

The mechanism for this step is a Hoffman rearrangement as shown in Figure 34. The hydroxide deprotonates the compound leaving the nitrogen with a negative charge which attacks the halogen. The hydroxide again deprotonates the compound creating a negatively charged nitrogen meaning it has a higher affinity for the electrons in the chiral carbon to bond with rather than its currently bonded carbon. This creates an isocyanate intermediate containing a partially positive carbon that the negatively charged hydroxide will attack creating a carboxylic acid intermediate. The hydroxide group then accepts the hydrogen leaving an unstable resonance which prefers to be in the form of carbon dioxide leaving a negative nitrogen to accept a hydrogen from water giving the primary amine (66).

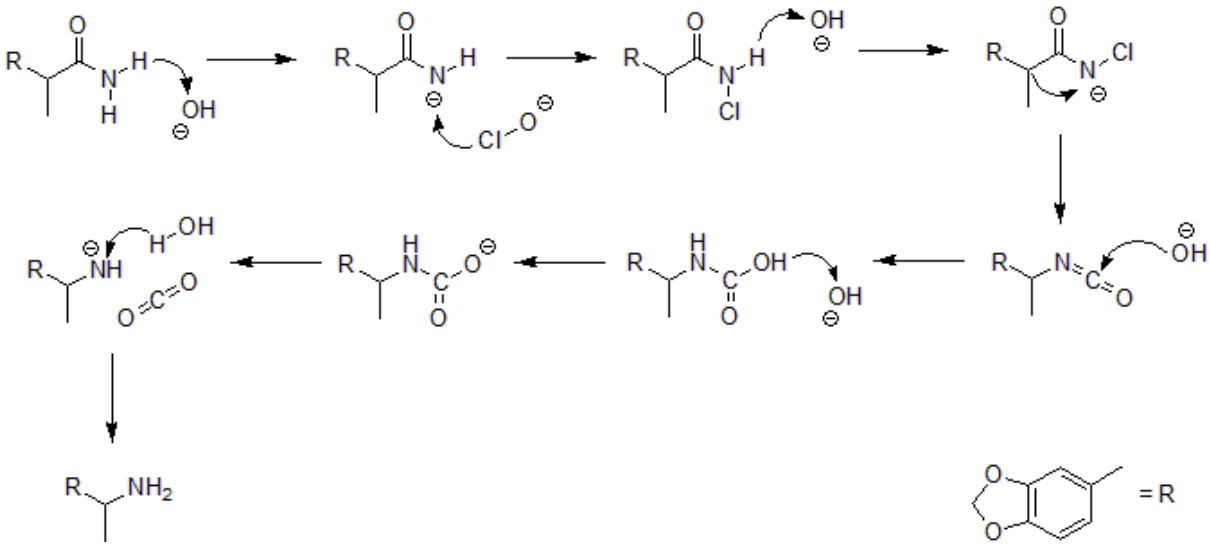
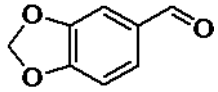
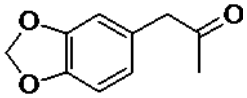
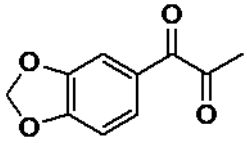
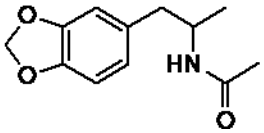
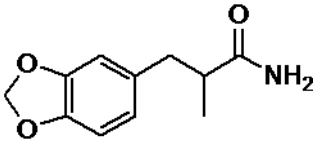
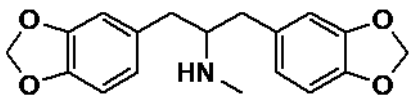


Figure 34: Mechanism of the synthesis of MDA free base from MMDPPA

This product was consistently a dark brown oil. The crude molar yield for this step was about 70%. The impurities that were identified were consistently present in the 3 repeats to the free base product and are summarised below in Table 6.

Table 6: Summary of impurities found in the amine free base of the synthesis of MDA from helional.

Compound		Name	m/z	rt	1	2	3
1		Piperonal	149, 150, 121, 63, 65, 91	6.209m	X	X	X
2		MDP2P	135, 178, 77, 136, 51, 105	6.911m	X	X	X
3		MDP23P	149, 121, 65, 63, 192, 150, 91	7.088m	X	X	X
4	UNIDENTIFIED 2		147, 190, 89, 117, 63	7.167m	X	X	
5	UNIDENTIFIED 3		135, 44, 136, 77, 189, 179	7.302m	X	X	X
6		N-(2-Benzo[1,3]dioxol-5-yl-1-methyl-ethyl)-acetamide	162, 44, 135, 77, 86	7.931m	X	X	X
7		MMDPPA	135, 207, 77, 136, 105, 162	8.041m	X	X	X
8		(2-Benzo[1,3]dioxol-5-yl-1-benzo[1,3]dioxol-5-ylmethyl-ethyl)-methyl-amine	176, 135, 149, 77, 177	9.877m	X	X	X

The retention times mentioned in Table 6 refer to total times of 11.60 minutes. The mass spectrums of each impurity compound can be found in Appendix E. Compound 7 in Table 6 is MMDPPA, the amide intermediate, indicating that the reaction did not go to completion. Compounds 2-8 are reaction by-products that arose during this step, they have not been seen previously in the synthesis. Impurities 1-3 are potentially formed

through the hydrolysis of their respective carbons. Compounds 1 and 2 have been identified previously by Lukaszewski 1978 (49) as impurities present in MDA synthesized from safrole via the Leuckart Reaction. Compound 1 is piperonal, a commonly known starting material for the synthesis of MDA, and compound 2 is MDP2P, also a commonly known precursor for the synthesis of MDA and an intermediate in the synthesis undertaken in this project of MDA from piperonal. The similar compound of MDP1P has been recorded by Swist et al 2005 as an impurity that arose during the synthesis of MDMA from isosafrole (67). Compound 3 has been identified by Swist et al 2005 as an impurity found during the synthesis of MDMA from piperonal. The acetamide structure seen in impurity 6 has also been documented to appear attached to a base structure within Stojanovska et al 2013. This particular impurity containing the acetamide group was found as a characteristic impurity indicating MDMA produced via reductive amination (34). This group was also found by Swist et al 2005 in the form of n-cyclohexyl-acetamide. They found this impurity carried through all 3 steps of the synthesis of MDMA from piperonal (67). Impurity 8 has been previously documented by Bohn, Bohn, Blaschke (42) as an impurity characteristic of the production of MDA using a Leuckart-Wallach synthesis from 3,4-(methylenedioxy)phenylacetic acid.

3.3.4 MDA HCl synthesis

The amine base was dissolved into dry diethyl ether and 1 ml of HCl in diethyl ether was then added to precipitate the amine salt. Then the solution was evaporated off. The amine salt was then washed with cold acetone and dried resulting in an off-white crystalline solid.

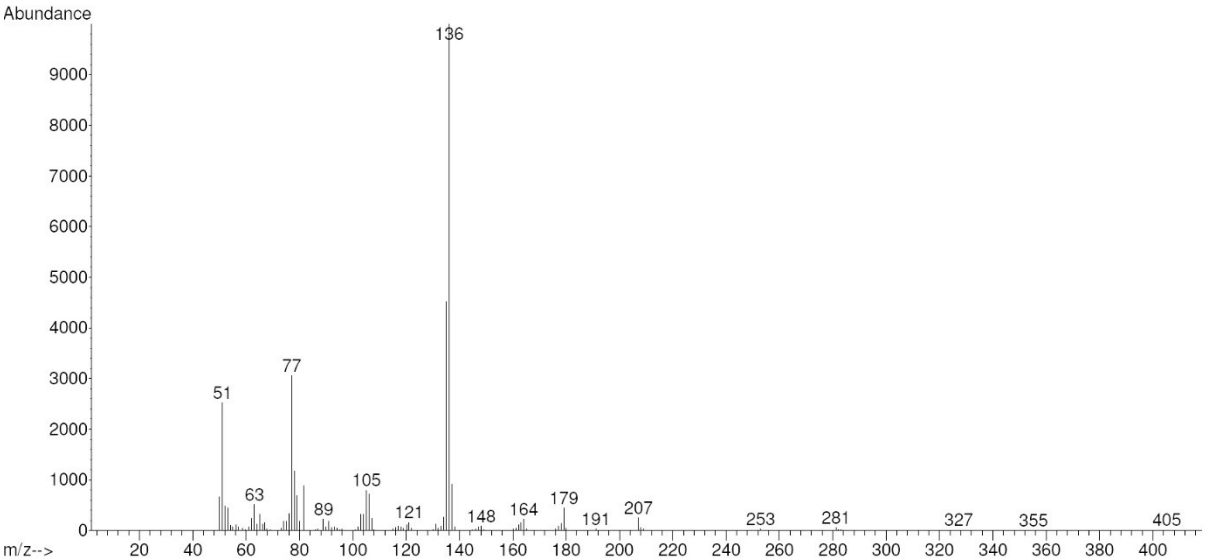


Figure 35: MS of MDA HCl

Figure 35 shows confirmation of the successful synthesis of the MDA HCl product. The purified yield for this step ranged from 10-20%. This is potentially lower than it should be due to the scale of the reaction undertaken. Because there was such a small amount of product any loss due to partial solubility or glassware transfer would have had a larger effect on the final yield.

The GCMS results of the MDA HCl were poor and no impurities were able to be identified. To overcome this a derivatisation of the products was undertaken with ethyl chloroformate (eCF). A standard was made of 1000 ppm MDA HCl in methanol, MDA HCl was insoluble in ethyl acetate. A stock was made of 5 µl of eCF in 10 ml of ethyl acetate. A sample was made of 100 µl of the MDA HCl standard, and 30 µl of the eCF stock solution, this was heated for 10 minutes at 65°C. This was then run through the GCMS. The resulting chromatogram showed more peak definition at higher concentration and a more even base line, however this did not lead to any impurities being identified. This can be seen in the comparison of Figure 37 and Figure 38 where the former is the derivatised product and the latter the HCl product.

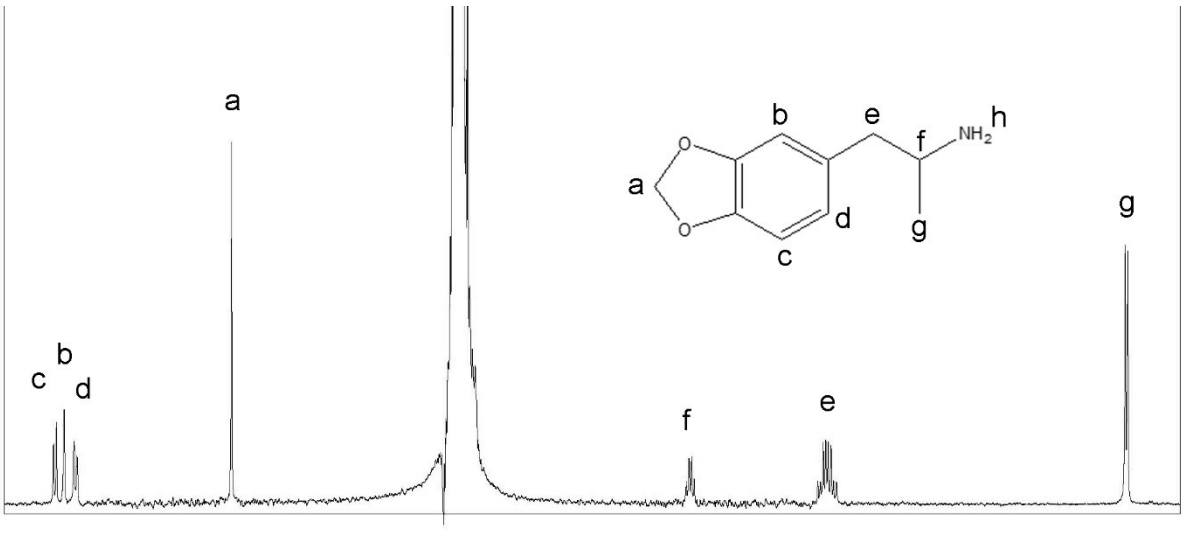


Figure 36: ^{1}H NMR of MDA HCl with peak allocation of the different hydrogen environments within the molecule.

Table 7:Chemical Shift values for peak in ^{1}H NMR of MDA HCl

Peak	Chemical Shift (δ)	Multiplicity	No. of Protons
a	5.98	Singlet	2
b	6.86	Singlet	1
c	6.91, 6.90	Doublet	1
d	6.80, 6.79	Doublet	1
e	2.92, 2.91, 2.89, 2.88, 2.87, 2.85, 2.84, 2.83	Multiplet	2
f	3.61, 3.60, 3.58, 3.57	Quartet	1
g	1.32, 1.30	Doublet	3

Figure 36 confirms the purity of the HCl product, it shows the ^{1}H NMR spectrum with peak allocations for the different hydrogen environments and demonstrates the lack of extraneous peaks that indicate the presence of impurities. The NMR chemical shift values are shown in Table 7. To confirm this analysis a derivatisation of the HCl product was undertaken as per the procedural outline previously mentioned in section 3.3.4. This derivatisation with ethyl chloroformate yielded no additional results. Figure 37 shows the gas chromatograph of the derivatised product- the main peak being the product peak. However, the extra peaks present were also present in the blank still giving no identifiable impurities in the HCl product.

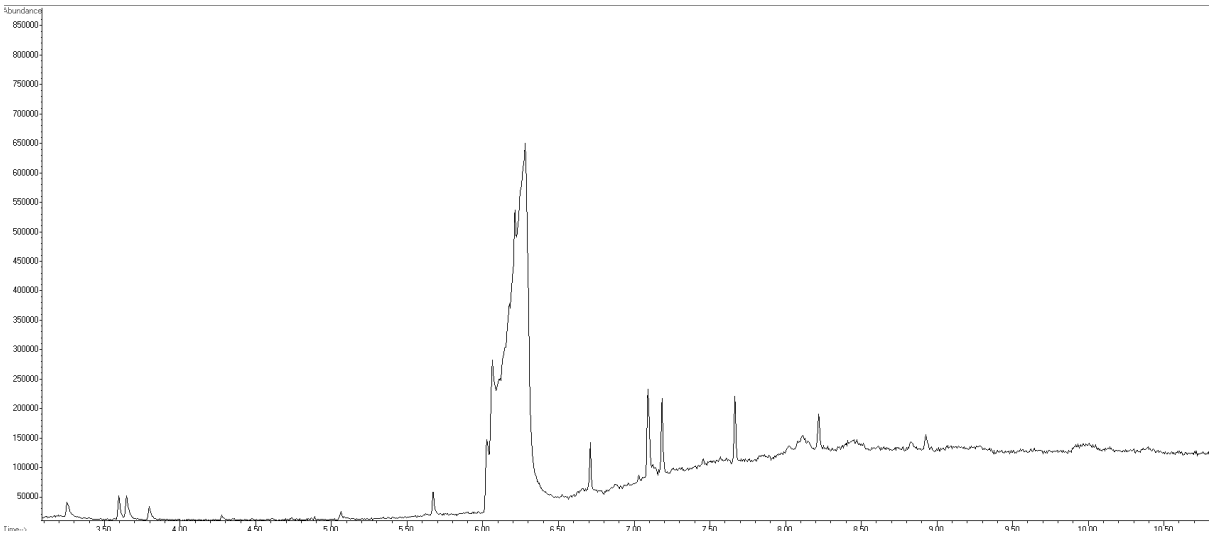


Figure 37: Gas Chromatograph of the derivatised MDA HCl product

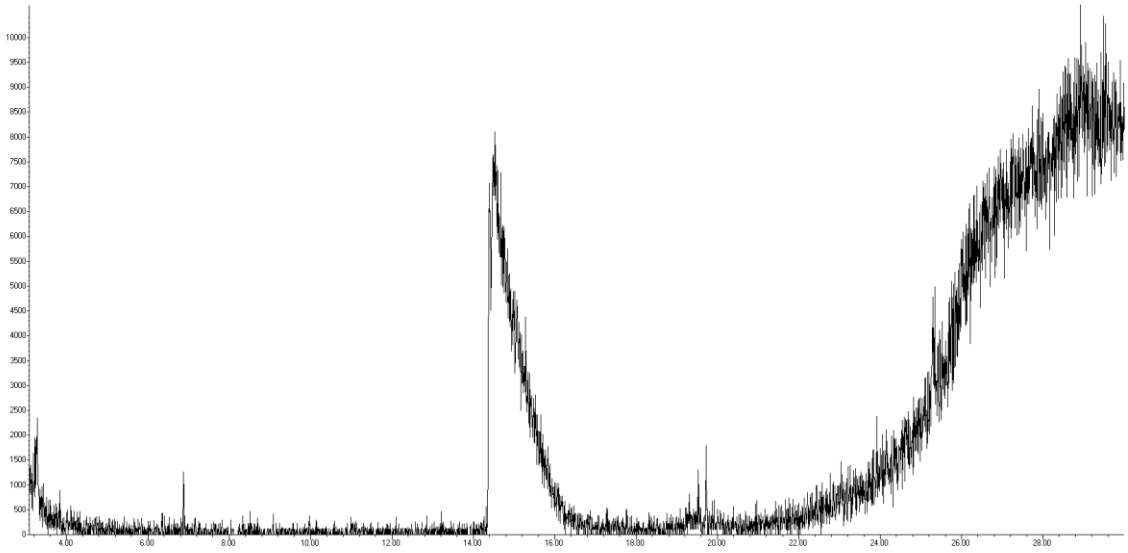


Figure 38: Gas Chromatograph of MDA HCl before derivatisation of product.

3.4 Synthesis of MDA from Piperonal

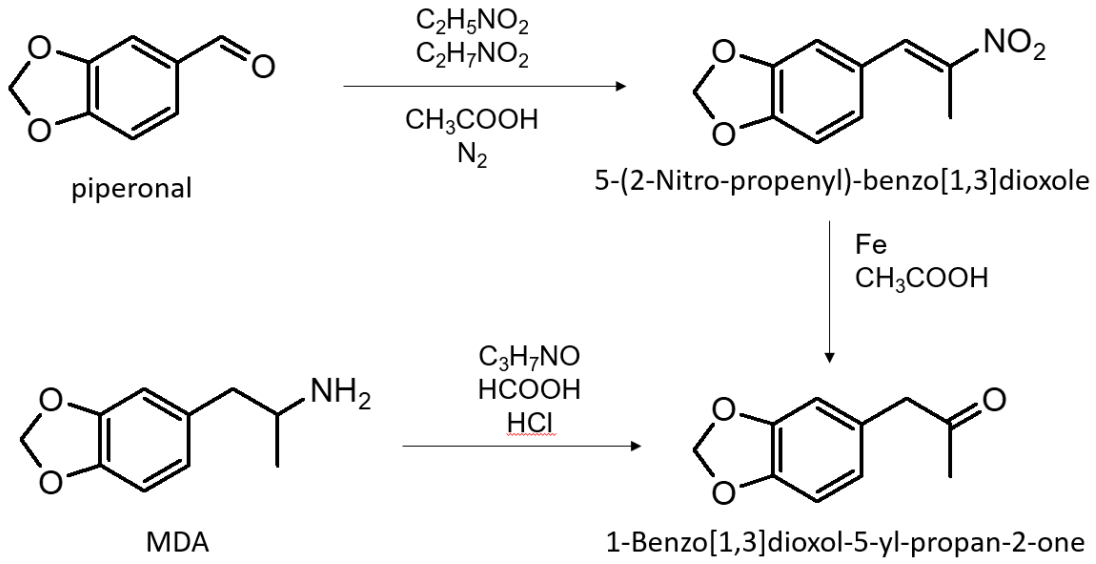


Figure 39: Synthesis of MDA from piperonal

The synthesis of MDA from piperonal as outlined in Figure 39 has been adapted from Tam et al(40). This route has been modified since the original plan as will be discussed in section 4.1. This route has been chosen due to the availability of reagents. Piperonal as a starting material, although a control substance in itself, can be extracted from black pepper however this has been demonstrated to produce poor purified yields of about 3% pepper to MDA(41). It is a good comparison method because piperonal is a well-known

starting material. GC and NMR data for the precursor and the products of each step are available in Appendix B and C respectively.

3.4.1 Synthesis of 5-(2-Nitro-propenyl)-benzo[1,3]dioxole from piperonal

The synthesis of the nitrate from piperonal results in a bright orange solid, this colour exhibited minor variation ranging from a yellow-orange to a dark orange. The more yellow colour is indicative of the reaction not running to completion. The crude molar yield for this step was around 90%. The GC data is available in Appendix B and the NMR spectra available in Appendix C.

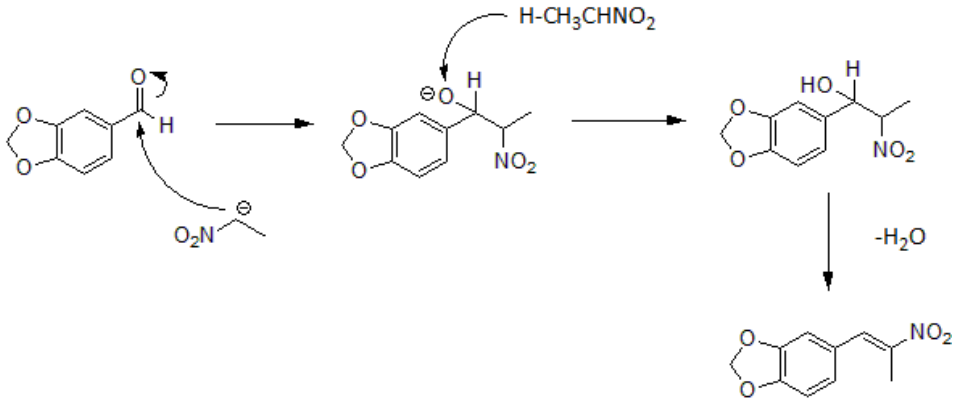


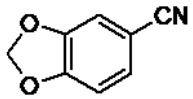
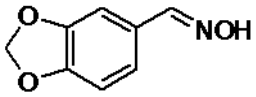
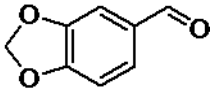
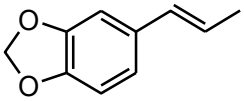
Figure 40: Mechanism for the synthesis of 5-(2-nitro-propenyl)-benxo[1,3]dioxole from piperonal

The proposed mechanism for the production of the nitrate is a Henry reaction as outlined in Figure 40. The negatively charged nitrate molecule attacks the partically positive carbon leading to the production of the nitro alcohol. This is then dehydrated to form the nitrate (68). Confirmation of the synthesis of the product is shown the NMR chemical shift values in Table 8.

Table 8: Chemical Shift values for peak in ^{1}H NMR of 5-(2-nitro-propenyl)-benzo[1,3]dioxole

Peak	Chemical Shift (δ)	Multiplicity	No. of Protons
a	6.05	Singlet	2
b	6.97	Singlet	1
c	6.99, 6.97	Doublet	1
d	6.90, 6.88	Doublet	1
e	8.02	Singlet	1
f	2.46	Singlet	3

Table 9: Summary of impurities found in nitrate intermediate of the synthesis of MDA from piperonal.

Compound		Name	m/z	rt	1	2	3	4	5
1		piperonylonitrile	146, 147, 62, 63, 89	5.438m	X	X	X	X	X
2		1,3-benzodioxole-5-carboxaldehyde, oxime	165, 122, 121, 146, 63, 137	5.899m	X	X	X	X	X
3		piperonal	149, 150, 121, 63	6.503m			X	X	X
4		isosafrole	77, 104, 131, 146, 162	6.610m				X	X

The retention times mentioned in Table 9 refer to total run times of 11.60 minutes. The mass spectrums of each impurity compound can be found in Appendix F. Compound 1 as shown in Table 9 is piperonylonitrile. Compound 2 is 1,3-benzodioxole-5-carboxaldehyde, oxime. Compound 3 is piperonal the starting material that has been left unreacted. All 3 of these compounds were found in Swist et al. 2005 as an impurity within their synthesis of MDA from piperonal. Compound 4 is isosafrole in accordance with the identification done by Swist et al. 2005 where they found the compound as an impurity in MDMA synthesized from isosafrole (67).

3.4.2 Synthesis of 1-Benzo[1,3]dioxol-5-yl-pronan-2-one (MDP2P) from 5-(2-Nitro-propenyl)-benzo[1,3]dioxole

The product of the ketone synthesis from the nitrate was consistently a dark brown oil. The extraction of the ketone from the solution was prone to creating a large emulsion making extraction more difficult and potentially losing some product during it. The crude molar yield for this step was then around 70%. The GC data is available in Appendix B and the NMR spectra available in Appendix C

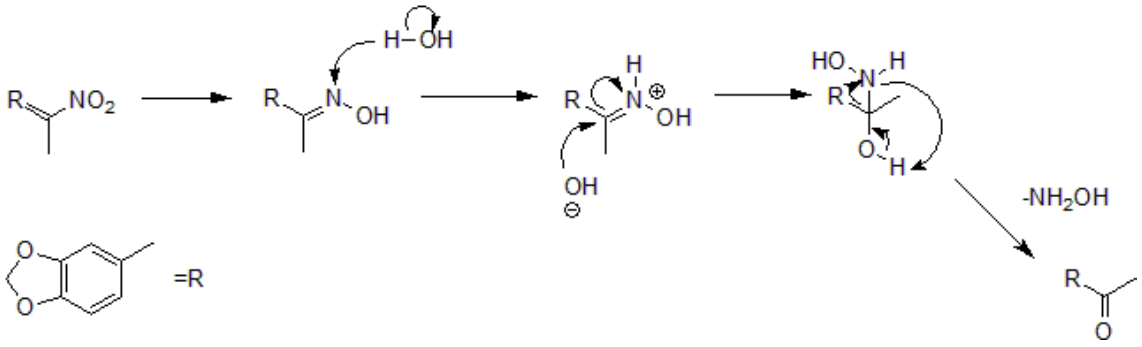


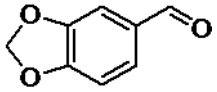
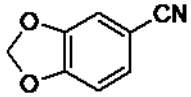
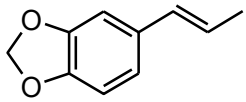
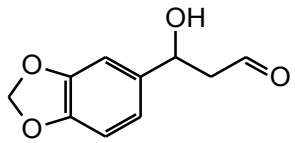
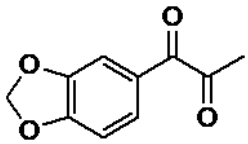
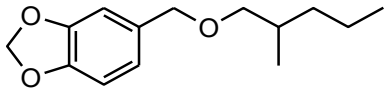
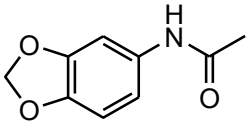
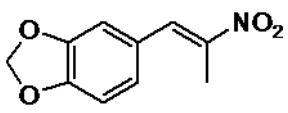
Figure 41: Mechanism for MDP2P synthesis from 5-(2-nitro-propenyl)-benzo[1,3]dioxole

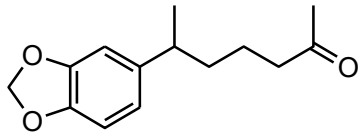
The proposed mechanism for the production of MDP2P from 5-(2-nitro-propenyl)-benzo[1,3]dioxole is shown in Figure 41. The protonation of the nitrogen leads to it reclaiming the electrons from the double bond allowing for the bonding of the hydroxyl group onto the carbon. The hydroxyl group is then deprotonated creating the ketone and expelling the oxime (68). The ^{1}H NMR chemical shifts for the product of this step are shown in Table 10.

Table 10: Chemical Shift values for peak in ^{1}H NMR of 1-Benzo[1,3]dioxol-5-yl-propan-2-one

Peak	Chemical Shift (δ)	Multiplicity	No. of Protons
a	5.94	Singlet	2
b	6.67	Singlet	1
c	6.77, 6.75	Doublet	1
d	6.64, 6.63	Doublet	1
e	8.01	Singlet	1
f	3.59	Singlet	2
g	2.14	Singlet	3

Table 11: Summary of impurities found in ketone intermediate of the synthesis of MDA from piperonal.

Compound		Name	m/z	rt	1	2	3	4	5	6	7
1		piperonal	149, 150, 121, 63	6.523m	X	X	X	X	X	X	X
2		piperonylonitrile	146, 147, 62, 63, 89	6.551m		X	X	X	X		X
3		isosafrole	162, 104, 131, 103, 161, 77. 146	6.613m		X	X				
4		3-Benzo[1,3]dioxol-5-yl-3-hydroxy-propionaldehyde	135, 194, 152, 77, 134, 178	6.978m	X	X	X	X			X
5		1-Benzo[1,3]dioxol-5-yl-propane-1,2-dione	149, 121, 65, 63, 150, 192, 91	7.085m	X	X	X	X	X	X	X
6	UNIDENTIFIED 4		204, 161, 103, 131, 77, 43	7.355m	X	X	X				
7		5-(2-Methyl-pentyloxymethyl)-benzo[1,3]dioxole	151, 193, 93, 43, 149, 236	7.563m		X	X		X		
8		N-Benzo[1,3]dioxol-5-yl-acetamide	137, 179, 149, 165, 79	7.594m		X	X				X
9		5-(2-Nitro-propenyl)-benzo[1,3]dioxole	103, 160, 207, 77, 102	7.872m	X	X	X		X	X	

10	UNIDENTIFIED 5		228, 146, 227, 145, 229, 160	7.974m		X			X		X
11		6-Benzo[1,3]dioxol-5-yl-heptan-2-one	150, 192, 43, 93, 151	8.007m	X	X	X				X
12	UNIDENTIFIED 6		151, 44, 220, 86, 150, 87, 43	8.392m	X		X				X
13	UNIDENTIFIED 7		310, 267, 209, 237, 150	10.065m	X	X	X		X		X

The retention times listed in Table 11 refers to a total run time of 11.60 minutes. The mass spectrums of each impurity compound can be found in Appendix G. Compounds 1 (piperonal), 2 (piperonylonitrile), and 3 (isosafrole) were all seen in the previous nitrate intermediate, already this synthesis route is showing more carry-through of impurities than the synthesis of MDA from helional. Compound 5 has been identified in MDMA synthesised via reductive amination with Al/Hg (69) and MDP2P synthesised from piperonal (67). A similar structured impurity to compound 8, with the same acetyl group, was listed as an impurity found in MDMA synthesised by reductive amination (34). Compound 9 is the nitrate intermediate persisting through the reaction. Compounds 6, 10, and 12 could not be identified but the mass spectrum for each has been included as a unique characteristic for these compounds. Compounds 7 and 11 both are characterised by the addition of a carbon chain, the source of these impurities are unknown however the addition of extra carbon rings is common throughout the aforementioned articles and reviews.

3.4.3 Synthesis of MDA from 1-Benzo[1,3]dioxol-5-yl-pronan-2-one

The product was a dark brown oil. A place that did show a colour variation was during the extraction with dichloromethane where in one of the samples the organic layer had a pink tinge to it rather than the usual yellow. The impurities found in the free base product are summarized in Table 12.

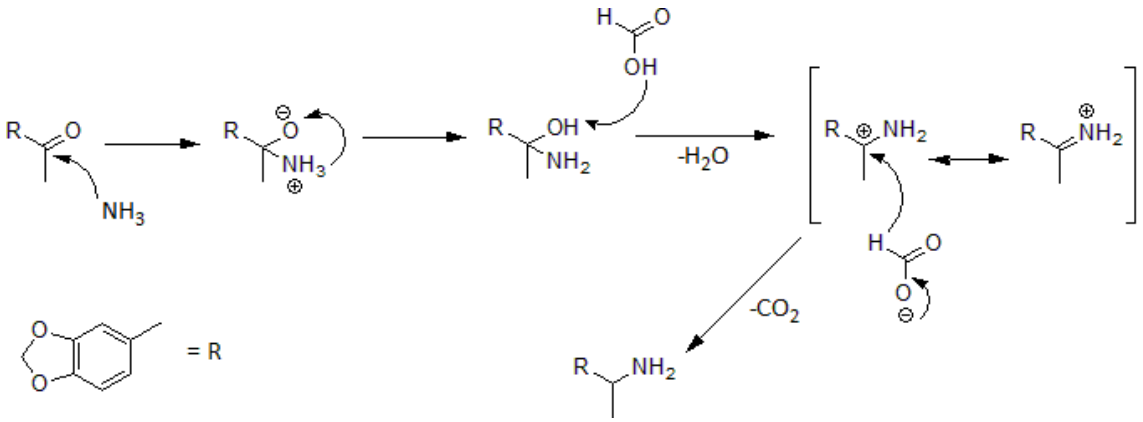


Figure 42: Mechanism for the synthesis of MDA from MDP2P

The proposed mechanism for this reaction is a Leuckart reaction (62). As shown in

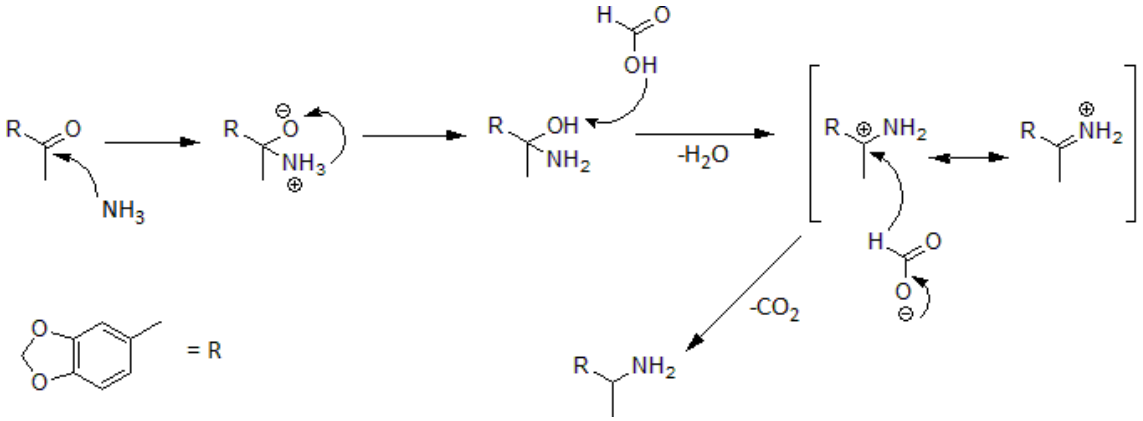
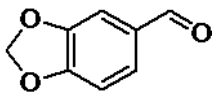
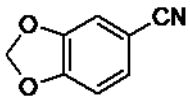
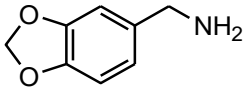
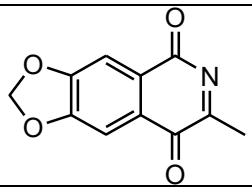
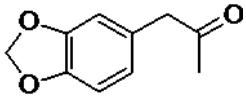
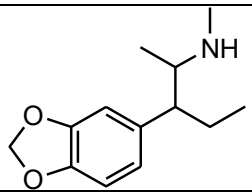


Figure *42*, the ammonium makes a nucleophilic attack on the central carbon and one of those hydrogens moves to the oxygen. The new hydroxyl group then accepts a hydrogen from a formate molecule departing as water. This leaves a resonance structure, one of which accepts the hydrogen from a deprotonated formate molecule leaving the amine product and a carbon dioxide by-product.

Table 12: Summary of impurities found in amine free base product of the synthesis of MDA from piperonal.

Compound		Name	m/z	Rt	1	2	3
1		Piperonal	149, 150, 121, 63	5.622m	X	X	
2		piperonylonitrile	146, 147, 62, 63, 89	5.632m	X	X	X

3		piperonylamine	149, 150, 121	5.673m	X		X
4		7-Methyl-[1,3]dioxolo[4,5-g]isoquinoline-5,8-dione	57, 135, 191, 206	6.788m	X	X	X
5	UNIDENTIFIED 8		214, 213, 155	6.927m	X	X	X
6	UNIDENTIFIED 9		202, 201, 143	7.663m		X	X
7	UNIDENTIFIED 10		216, 215, 117, 218	7.710m	X	X	X
8	UNIDENTIFIED 11		176, 149, 207, 135, 177	8.907m	X		X
9		MDP2P	135, 178, 77, 136	9.057m		X	X
10		(2-Benzo[1,3]dioxol-5-yl-1-methyl-butyl)-methyl-amine	163, 206, 135, 105, 77	9.280m	X	X	X
11	UNIDENTIFIED 12		135, 162, 77, 136	11.151m		X	X

The retention times listed in Table 12 refer to total run times of 16.80 minutes. The mass spectrums of each impurity compound can be found in Appendix H. Compounds 1, 2, and 9 are impurities that have been seen in previous steps. Compound 1 is the piperonal starting material that has carried all the way through the synthesis. Compound 2 is the

cyanonitrate impurity that has also been present throughout the synthesis. Compound 9 is the ketone intermediate and has carried through to the final product of the amine free base. Compound 4 has been previously found in MDMA synthesized from piperonal by Swist (67). The methylated version (3,4-methylenedioxy-N-methylbenzylamine) of compound 3 (piperonylamine) has been seen across studies of MDMA (37, 45, 69). It should be expected therefore, that since an amphetamine rather than a methamphetamine is being synthesized that impurities would also be primary amines rather than secondary amines. Compound 10 was identified because the mass spectrum was given by Gimeno (44) who found it as an impurity is seized MDMA tablets.

3.4.4 Alternative MDA from piperonal synthesis methods

It was attempted to skip the second step of the piperonal synthesis and go straight from 5-(2-Nitro-propenyl)-benzo[1,3]dioxole to MDA. 5-(2-Nitro-propenyl)-benzo[1,3]dioxole (100 mg) was dissolved in dry ether (10 ml) and lithium aluminium hydride (70.5 mg) was added. The mixture was refluxed for 20 hours and then allowed to cool. The reaction was then quenched by adding water and the excess metal filtered out and washed with ether. The product was extracted with ether, washed with water, and dried with anhydrous sodium sulfate. HCl in ether (1 ml) was added the solvent evaporated off (49). The product was analysed by NMR spectroscopy giving results that are consistent with the nitrate starting material. No reaction was observed.

The third step of the piperonal synthesis, from MDP2P to MDA, was attempted using the following method. The ketone product, n,n-dimethylformamide (2 ml), and formic acid (1 ml) were combined and refluxed at 150°C overnight. After it had cooled HCl (2 ml, 5M) was added and the solution was put on reflux overnight at 150°C. After it has cooled ammonium hydroxide was slowly added until the solution was basic. The product was then extracted with dichloromethane and the solution dried with anhydrous sodium sulfate. The solvent was then evaporated off using the rotary evaporator leaving the product in the form of a dark brown oil (40). This process resulted in the following mass spectrum: M/z: 135, 179, 136, 178, 77, 58, 51, 105, and the NMR spectrum shown in Figure 43.

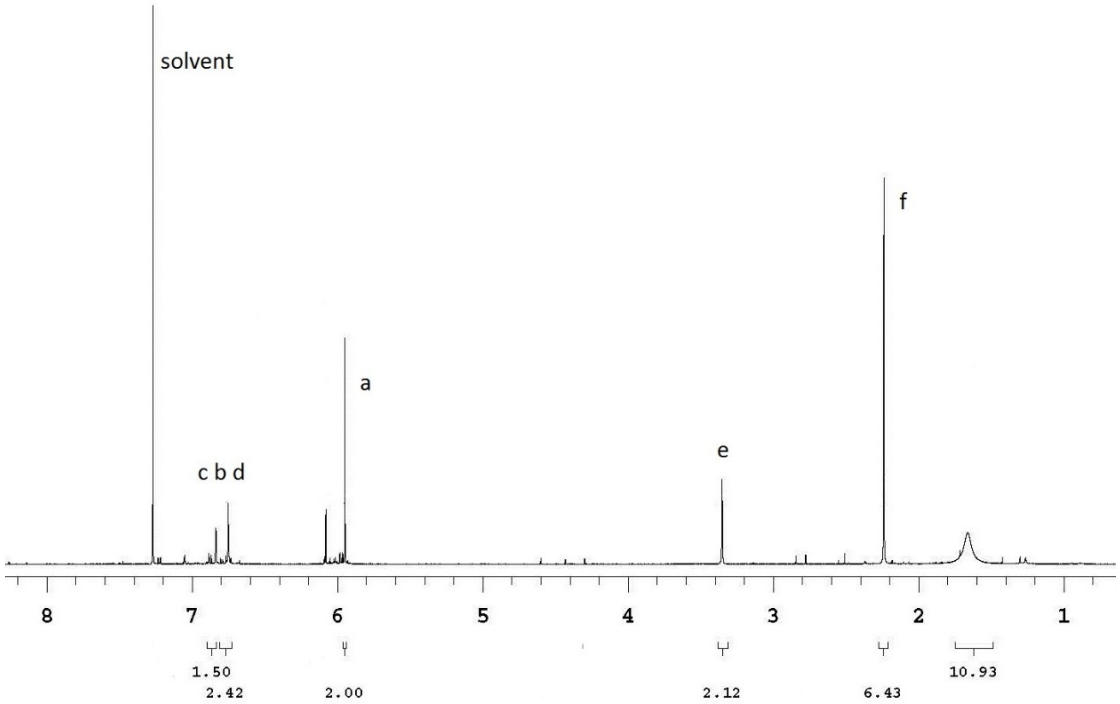


Figure 43: ^{1}H NMR Spectrum of 3,4-Methylenedioxy-N,N-dimethylbenzylamine

The product of this method was then identified to not be MDA but to be 3,4-Methylenedioxy-N,N-dimethylbenzylamine the structure of which is shown in Figure 44. The hydrogen environments labelled correspond to the labelling of the peaks in Figure 43. The mechanism behind this product is also the Leuckart reaction proposed in

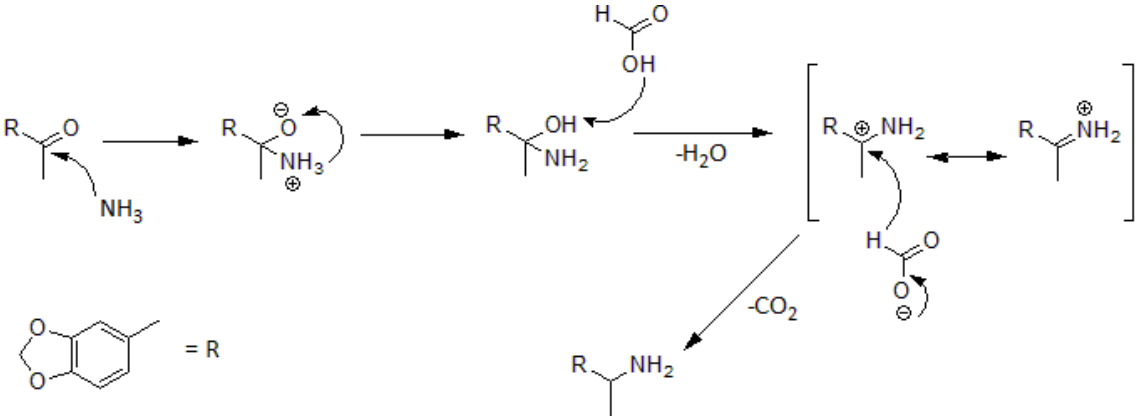


Figure *42* except rather than the primary amine used in the initial step, a tertiary amine was used resulting in a tertiary amine as the final product.

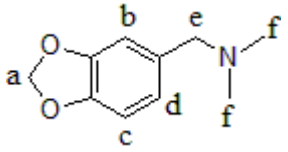


Figure 44: Structure of 3,4-Methylenedioxy-N,N-dimethylbenzylamine with hydrogen environments labelled

The third step of the piperonal synthesis was then attempted via the following method: the ketone product and an excess of ammonium formate was placed on reflux for six hours at 180°C then allowed to cool. HCl (30%, 5 ml) was added and the mixture heated under reflux for 3hrs (62). Afterwards, the resultant solution was allowed to cool, then water (5 ml) was added. NaOH pellets were added to the solution until alkaline. The product was then extracted with DCM, washed with water, dried with anhydrous sodium sulfate and the solution evaporated off. The product of this, however, could not be identified and gave no signals on the GCMS or ^{1}H NMR. This is potentially because the base was too strong and rather than deprotonating the product, completely degraded it as with any impurities in the mixture.

4. Discussion

4.1 Experiemental Considerations

The “2 dogz” method of MDA synthesis from helional was successfully replicated within this project and was found to be an easy and safe method to follow. The most specialised piece of equipment required in all the steps of the synthesis is a condenser, other glassware needed being round bottom flasks and beakers. All required temperatures are achievable on a stovetop- the maximum being 140°C. A rotary evaporator was available in the laboratory and was used to decrease time in the last step however its use is not necessary and one could easily leave the product to dry overnight. No steps are completed under nitrogen or any other gas, this makes it relatively safe as no one is dealing with any compressed gasses. Except for the flammable nature of xylene and diethylether, the solvents used in the synthesis were low risk however, naked flames are not necessary lowering the risk associated with these liquids. The solvents used in the reactions were water, ethanol, and xylene and the liquid extractions were done with water and diethylether- a non-toxic solvent.

As mentioned previously, none of the steps are required to be done under nitrogen or another gas, this is significant to clandestine laboratories when it comes to avoiding raising suspicion. Purchase and transport of large quantities of gases is something that is monitored by police to identify suspicious behaviour and potential illegal drug manufacture. The bulk purchase of any of the other reagents by themselves, would also not be enough to raise suspicion as they can be easily bought through legitimate means. Nickel acetate is the hardest to acquire of all the reagents, however nickel acetate solution is commonly used for nickel plating and therefore both it and instructions to make it are available online. It can be easily made from both pure nickel and nickel oxide, nickel oxide is preferred as it is cheaper to buy and everything else needed for the transformation is available in a supermarket. To make it from nickel oxide all that is needed in acetic acid or vinegar and heat (60), however instructions for a nickel acetate solution from pure nickel is easily found on the internet because of nickel plating, from which the solution can be evaporated leaving the solid (70). The synthesis of nickel acetate was not undertaken in this study, analytical grade reagent was used.

The overall purified yield of the synthesis is 5-10% with a 50% yield of the amide and a 10-20% purified yield of the final MDA HCl. Given the proposed mechanism for the production of the amide there is very little chance of increased yield through methodology

at that point. However, there is a potential for increased yield during the synthesis of the MDA free base and the recrystallisation of the HCl salt. Due to the small scale of the reaction undertaken, loss due to glassware transfer and solubility limits would have had effect on the yield. The small amounts that get left in glassware, or fail to crystalize, would be a larger percentage of the total product in these reactions than it would be in a clandestine laboratory which makes amounts larger by whole orders of magnitude. Having potential yields ranging from 20-50% makes this synthesis method a worthwhile endeavour for clandestine laboratories who seek to produce MDA.

The only issue that was found within the synthesis itself was that the reaction would sometimes fail to proceed to the next step. The reason for this was determined to be because the temperature was to low and failed to reach the required temperature. The step involving the synthesis of MMDPPA was particularly subject to this fault as it requires the highest temperature. There is a reason the solvent being used is xylene rather than the similar, safer, and more readily available toluene. This is because the boiling point for toluene is lower and unable to reach the 140°C required for the reaction to proceed.

The procedure for the synthesis of MDA from piperonal by comparison is slightly more difficult and dangerous. This synthesis requires that the first step be completed under nitrogen which can be difficult and conspicuous to come by. It requires slightly higher temperatures than the helional synthesis needing 180°C for the conversion of MDP2P to MDA with all the steps requiring heat to some capacity. The solvents and reagents used for the synthesis of MDA from piperonal are not as safe. All the extractions are to be done with dichloromethane which is toxic, while also multiple steps involve the use of acids and bases of high concentration in the form of acetic acid, ammonium hydroxide, and hydrochloric acid. This synthesis would not be as inconspicuous as the helional synthesis due to the use of gas cylinders as mentioned previously, but also piperonal itself is a controlled substance and unable to be obtained through legitimate means. If a clandestine chemist wanted to avoid the procuring of piperonal, an extraction from black pepper of piperine with a subsequent conversion to piperonal is possible however it greatly decreases the yield of the entire synthesis. This would take the purified molar yields from around 50% for piperonal to MDA to about 3% for pepper to MDA (41).

4.2 Synthesis Comparison

A cost analysis was undertaken to compare the cost versus the potential income of the two methods. An arbitrary theoretical amount of $10,000 was used for the calculations. The following calculations in

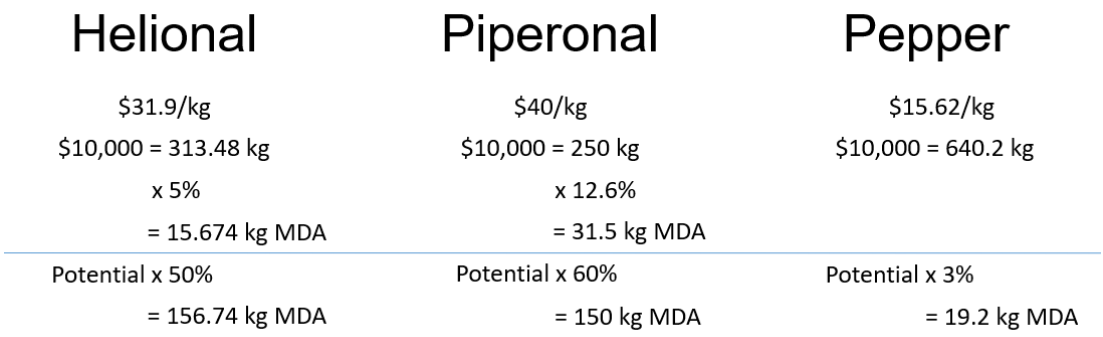


Figure *45* demonstrate how much of each starting material $10,000 can buy, how much MDA can be produced from that based on experimental yields, purified yield for MDA HCl synthesized from helional and crude yield for MDA base synthesized from piperonal.

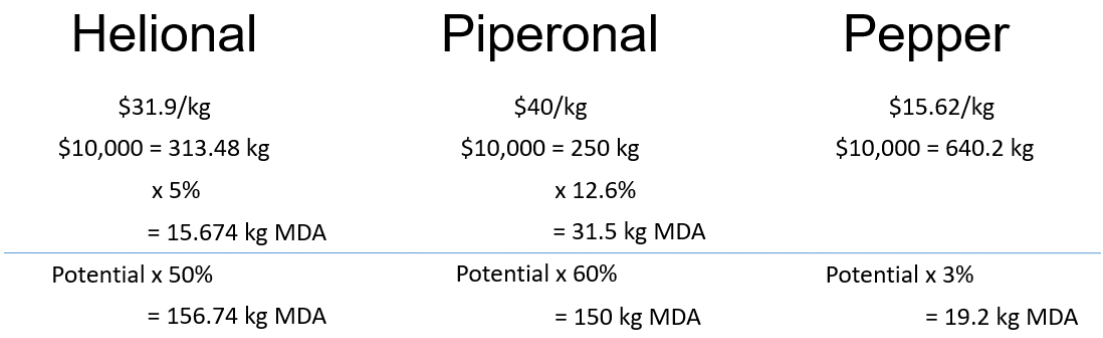


Figure 45: Cost analysis of different MDA synthesis methods

That the piperonal synthesis would make almost twice as much product as this new method is very surprising however like is not being compared with like in this circumstance. The helional product was taken through to the HCl salt whereas the piperonal product was only taken to the free base product and it is in the precipitation out of the ether where potential loss due to partial solubility would occur. But also, as previously mentioned, the experimental yields in this project were much lower than they could potentially be if the synthesis was undertaken on a larger scale. The calculations also include the amount of product at a reasonable potential yield for the synthesis, this result in roughly equal amounts of product. However, piperonal is a restricted compound and much riskier and more difficult to obtain. To reduce the risk involved in sourcing the

piperonal down to that of sourcing helional it must be extracted from another source. The price of pepper and the yield of MDA that results from the extraction and synthesis has been included for comparison purposes. As demonstrated the amount of resulting MDA is smaller by almost a whole order of 10.

The route of synthesis from helional to MDA is a viable option for clandestine chemists who don't wish to decrease their yields or put themselves in unnecessary danger of being caught by procuring illegal compounds. Instead, this method lets them slightly increase their yield while only buying completely legal ingredients.

4.2 Impurity Analysis

Route specific impurities can provide information to law enforcement agencies as to the method and staring material of the production of a drug sample. From this, law enforcement agencies can link samples, track and limit reagent and precursor supply, and generally uncover alternate investigation pathways otherwise unknown. Within this project, to determine the presence of a route specific impurity for MDA synthesized from helional the compounds identified within the product must be compared to the impurities identified in the MDA product of other synthesis methods. Impurities that carry through all the steps of the synthesis can be incredibly useful as they indicate specific steps or reactions further back in the process, for example the origin of the MDP2P precursor.

In the synthesis of MDA from helional the only times when a compound is present in multiple steps is when an intermediate compound is the product of one step and then found as unreacted starting material of the next step. Therefore, in the MDA free base, the only impurity that has carried through, and did not arise within that last step, is MMDPPA, the previous intermediate. Because of this, limited conclusions can be made regarding the starting material of the MDA. There were no impurities in the final product that suggest a source further back in the process than the amide intermediate. From this research, one can infer that a sample was synthesized from MMDPPA but one cannot infer that that compound was synthesized from helional without further investigation. However, it is possible to conclude based on the presence of that amide, that the MDA was synthesized from helional if that is the only synthesis that involves that amide as an intermediate and it is not identified as an impurity in other syntheses.

Of the published methods of MDA synthesis from safrole, isosafrole, piperonal, and 3, 4-(methylendioxy)phenylacetic acid, none of them use MMDPPA as an intermediate nor

have they identified this compound as one of their impurities (42, 49). However, an unusual synthesis method of MDA has been identified by Dal Cason et al. 2012 that uses MMDPPA synthesized from α-methyl-3,4-methylenedioxycinnamic acid in the synthesis of MDA (71).. However, without the impurity analysis of MDA synthesized from α-methyl-3,4-methylenedioxycinnamic acid and knowing if it has route specific impurities that always carry through the entire reaction, it cannot be distinguished if the MMDPPA was synthesized from α-methyl-3,4-methylenedioxycinnamic acid or helional. However, this is still a useful conclusion to be able to make.

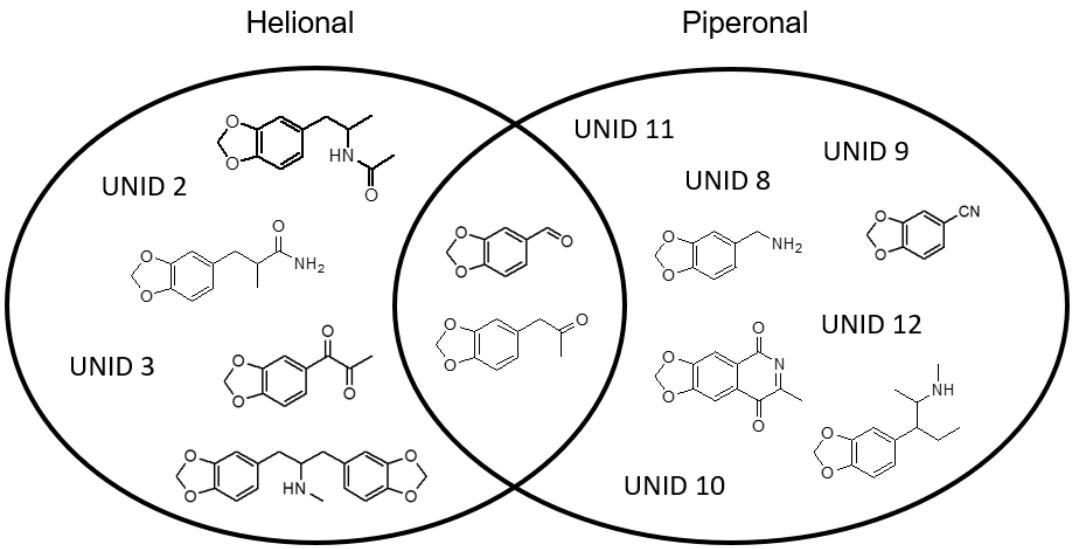


Figure 46: Comparison of impurities identified in the MDA free base products synthesized from Helional and Piperonal

A comparison of the impurities identified in MDA synthesized from helional to the impurities found in MDA synthesized from piperonal is shown in Figure 46. The impurities that arose within these routes were largely particular to one synthesis or the other, with the exception of piperonal and 1-(3,4-methylenedioxyphenyl)-1,2-propanedione which arose during both syntheses. The presence of piperonal, the comparison method's starting material, as an impurity in the helional synthesis shows that the presence of the starting material of a known synthesis method is not enough to conclude the method of synthesis for a particular sample as it is possible for it to arise as a by-product of alternate synthesis methods. 1-(3,4-methylenedioxyphenyl)-1,2-propanedione seems to be quite common as it has been recorded in synthetic routes of

MDMA from both piperonal and isosafrole (67), it is therefore reasonable for it to be present in the synthesis of MDA from helional as well.

Secondly, the impurities identified in MDA synthesized from helional was compared to those identified in the literature. There are limited articles on this topic with Lukaszewksi 1978, and Bohn, Bohn, and Blascke 1993 being the only ones that address the organic impurities found in MDA synthesized from various starting materials. Each impurity identified within the project's synthesis of MDA from helional has been addressed and compared to the impurities identified in these articles.

As already addressed, MMDPPA is an intermediate in the synthesis of MDA from α-methyl-3,4-methylenedioxycinnamic acid as recorded by Dal Cason 2012 (71). MDP2P was found as an impurity in MDA synthesized from 3, 4-(methylendioxy)phenylacetic acid, isosafrole, and piperonal. Piperonal was found as an impurity in MDA from piperonal. 1-(3,4-methylenedioxyphenyl)-1,2-propanedione has not previously been recorded as an impurity in MDA. N-(2-Benzo[1,3]dioxol-5-yl-1-methyl-ethyl)-acetamide has not been previous recorded as an impurity in MDA. The mass spectra of the unidentified compounds do not match any of the masses of previously recorded impurities in MDA. (2-Benzo[1,3]dioxol-5-yl-1-benzo[1,3]dioxol-5-ylmethyl-ethyl)-methyl-amine has been identified as an impurity in MDA synthesis from 3,4-(methylenedioxy)phenylacetic acid using a Leuckart-Wallach reaction (42).

This leaves N-(2-Benzo[1,3]dioxol-5-yl-1-methyl-ethyl)-acetamide and the unidentified compounds as potential route specific impurities. However, without knowing the structure of the unknown compounds a hypothesis about its origins and mechanics cannot be made, therefore there is not have enough information about these compounds to be able to conclude if they are route specific or not. The acetamide however may be, but it still does not give any information because it does not carry through from the free-base product to the HCl salt.

If the impurities that were identified in the free base product are scrutinised further, the lack of impurity carry through is not surprising. The HCl salt is precipitated from ether via protonation using HCl, therefore only compounds with primary or secondary amines would protonate leaving other impurities in the ether rather than the product. The amides would also fail to protonate due to the presence of the double bond oxygen which is preferred for protonation over the nitrogen. This leaves the two unidentified compounds

and (2-Benzo[1,3]dioxol-5-yl-1-benzo[1,3]dioxol-5-ylmethyl-ethyl)-methyl-amine as compounds potentially able to protonate and precipitate out of the ether. However, it is reasonable to think that the dimer is simply too large, even when protonated, to precipitate out with the product.

5. Conclusion

The aims of this project were successfully completed: The “2 dogz” method of synthesizing MDA from helional was replicated, confirming the production of MDA HCl as the final product. An organic impurity profile was created for the synthesis through the analysis and identification of the impurities found at each step of the synthesis.

The synthesis from helional to MDA viz the “2 dogz” method was completed proving the method to be a viable option to clandestine chemists for the production of MDA. It proved to be a simple method requiring only the glassware of a beaker, round bottom flask, and a condenser. It used limited toxic and corrosive solvents and reagents compared to the synthesis of MDA from piperonal, as well as not requiring any compressed gases or temperatures higher than those achievable of a stovetop. This study confirms the feasibility of this method previously only published on non-reputable sites and not in academic journals.

An organic impurity profile was created for the synthesis of MDA from helional. The product of each step was analysed using GCMS and ^{1}H NMR and the impurities identified. Multiple impurities were unable to be identified without further investigation, but this means that their mass spectrum does not match any of those of impurities previously seen in profiling studies regarding amphetamines. However, the mass spectrum is the information that is compared when analysing the organic impurity profile of a seized sample and that information is accessible should the compound appear as an impurity in seized samples.

No route-specific impurities were able to be identified for the synthesis of MDA from helional because none of the impurities identified carried through from the free base product to the hydrochloride salt. Through analysis by GCMS, ^{1}H NMR, and then further derivatization with ethyl chloroformate, still no impurities were able to be detected within any MDA HCl samples. The impurities detected in the free base product were either unable to precipitate out of ether or were soluble in acetone which purified the product.

Some of the impurity peaks in the gas chromatograph of MDA synthesized from piperonal were unable to be identified, the other ones had all been seen before in previous literature. The peaks were not able to be identified as the mass spectrums did not indicate the

presence of a methoxy or benzyl ring. Only piperonal and MDP2P were identified in MDA from both helional and piperonal.

5.1 Future Work

This opens the door for numerous furthur studies. Although clandestine manufacture was replicated as much as possible regarding methods and equipment, analytical grade reagents and precursors were used. Furthur study could be undertaken into the synthesis of MDA by the "2 dogz" method using commerical reagents and the impurities that arise during those synthesis due to impurities in the reagents and starting materials. All of the compounds needed for the synthesis can be purchased through legitimate means from home hardwares stores. These are the ingredients clandestine labs would have easy access to and therefore most likely use in their synthesis. The impurities in the reagents used could then potentially carry through and this could provide additional intelligence in the context of sample linkage and origin determination.

Furthur investigation into the profiles of seized street samples of MDA could provide additional comparisons for the potential identification of route specific impurites. We have previously seen in the impurity analysis of MDMA that both laboratory based synthesis analysis (27, 41, 43, 67) and the profiling of seized samples (35, 36, 38, 44) provide significant contribution to the knowledge pool and forensic intelligence in this area. Therefore, the same could be anticipated for research into seized MDA.

Thirdly, furthur analysis of laboratory synthesized MDA HCl by different analytical methods could prove more ideal for identifying links between samples and determining synthesis route, for example analysis by isotope ratio mass spectroscopy, or inorganic impurity analysis. Some repreats within the synthesis contained colour differences that did not affect the organic impurity profiles of the product, it remained unexplained by organic analysis however inorganic analysis could provide the answer. Isotope ratio analysis has already proved successful with MA analysis (33) and isn't limited by a pure product because it analyses the desired product. The information provided by these analytical methods, and potentially others, complement that provided by organic impurity analysis, this is valuable to forensic investigators.

Lastly, an article published by Dal Cason et. al 2012 was mentioned that contained a synthesis route to MDA from α-methyl-3,4-methylenedioxycinnamic acid. Their method contains MMDPPA as the immediate intermediate as does the helional synthesis. In light

of the the limited conclusions that can be made from the presence of MMDPPA in MDA in regards to the synthetic route, it would be enlightening to have Dal Carson's method profiled as well. Then the impurites could be compared and a more certain conclusion can be made, rather than the current speculation.

Appendix A- Gas Chromatographs

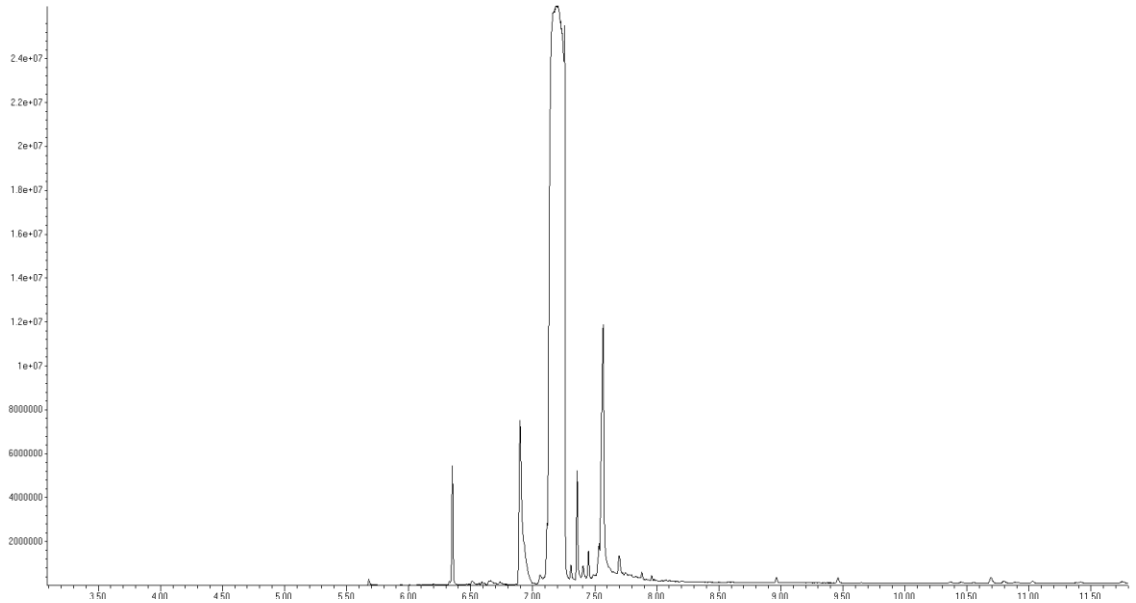


Figure A 1: Gas Chromatograph of helional precursor starting material

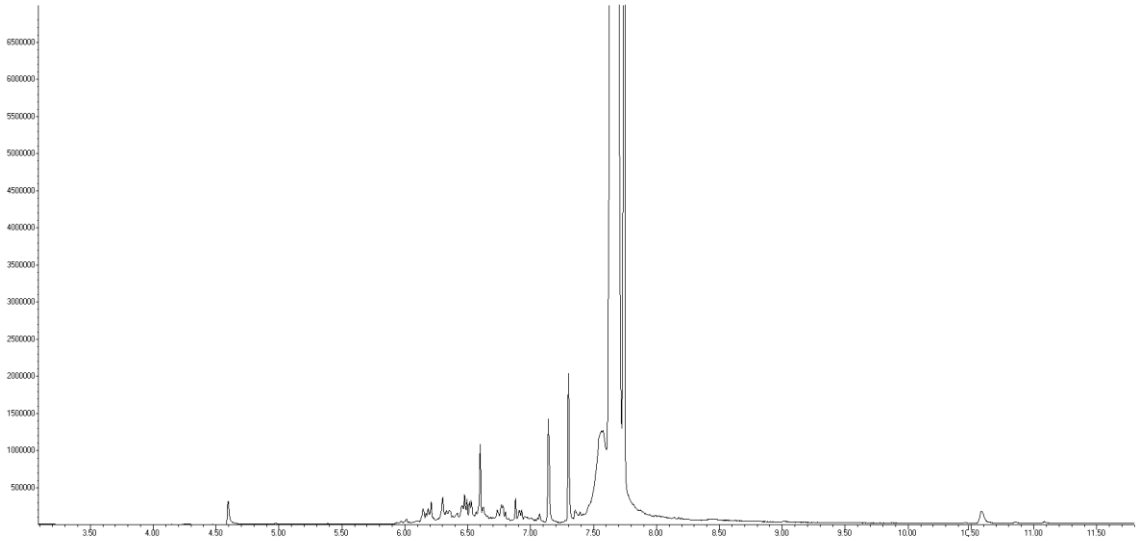


Figure A 2: Gas Chromatograph of 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime

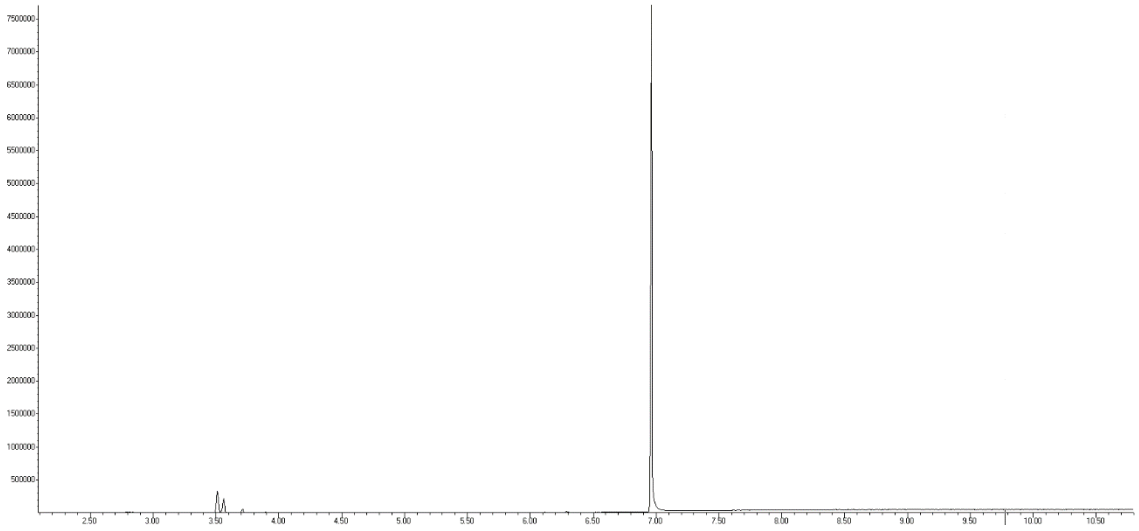


Figure A 3: Gas Chromatograph of MMDPPA

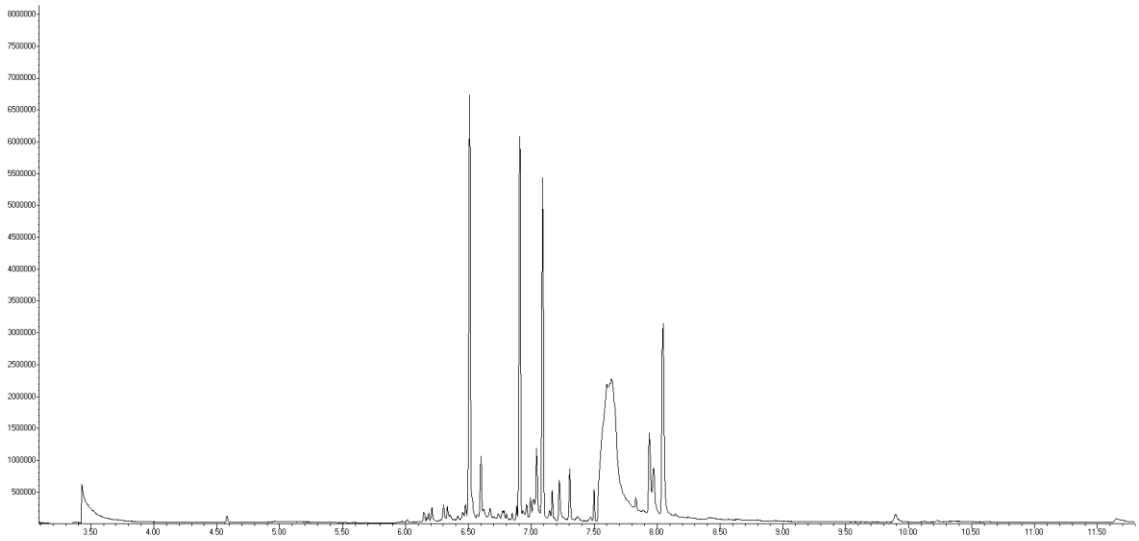


Figure A 4: Gas Chromatography of MDA free base synthesized from helional

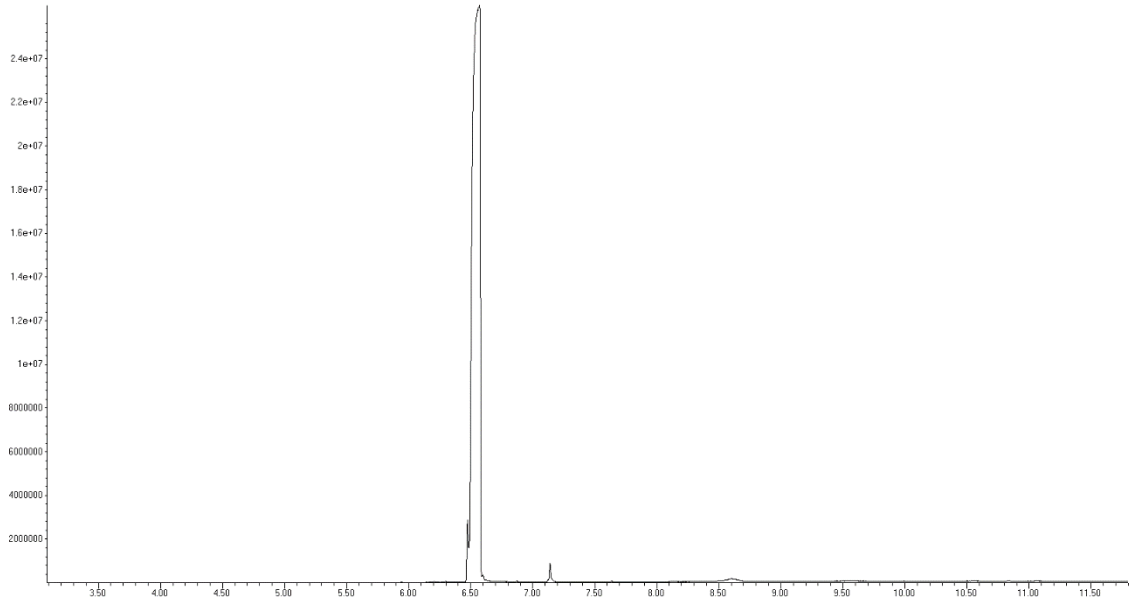


Figure A 5: Gas Chromatograph of piperonal precursor starting material.

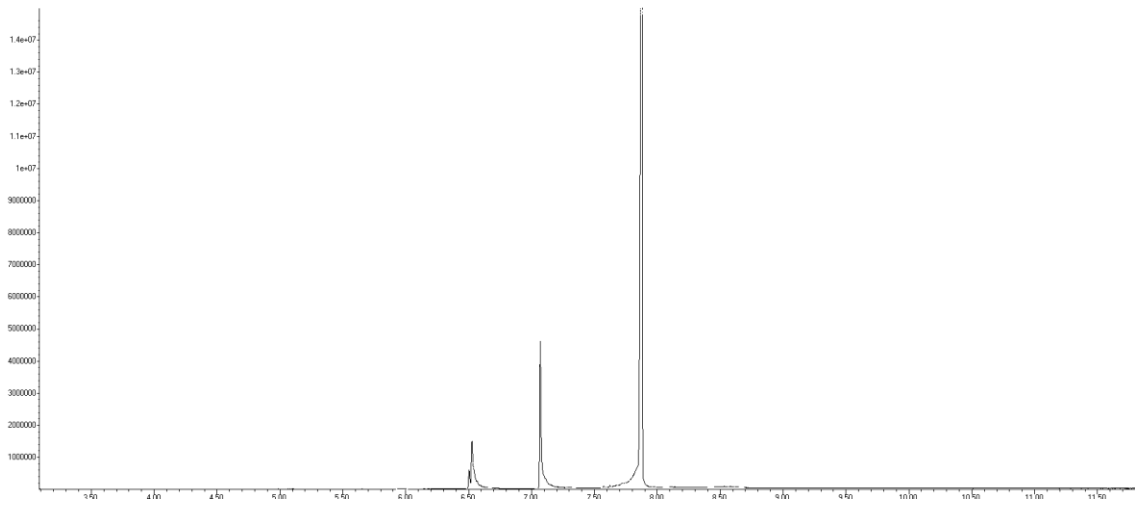


Figure A 6: Gas Chromatograph of 5-(2-nitro-propenyl)-benzo[1,3]dioxole.

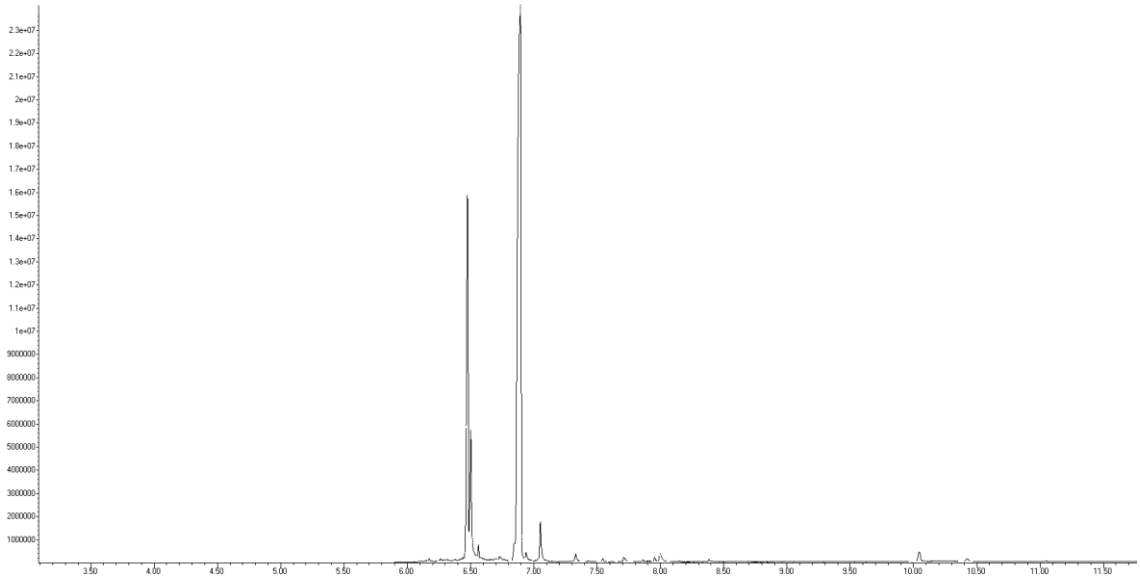


Figure A 7: Gas Chromatograph of MDP2P.

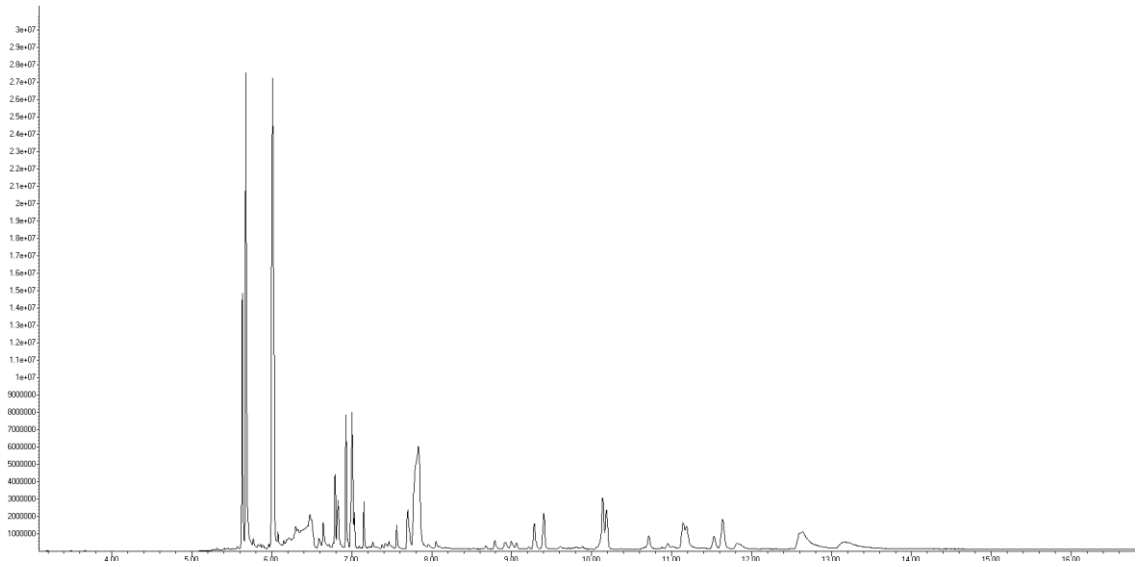


Figure A 8: Gas Chromatograph of MDA free base synthesized from piperonal

Appendix B- NMR Spectra

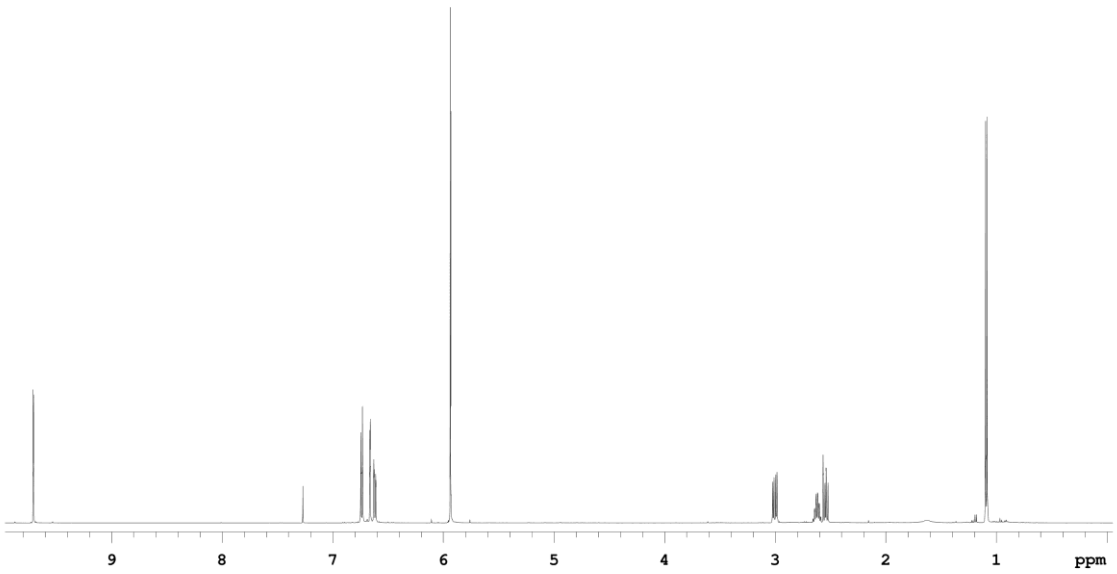


Figure B 1: ^{1}H NMR of Helional precursor starting material.

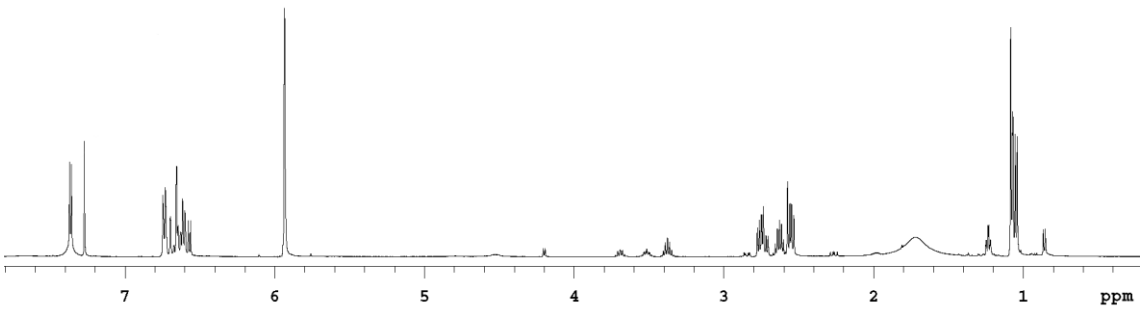


Figure B 2: ^{1}H NMR of 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime

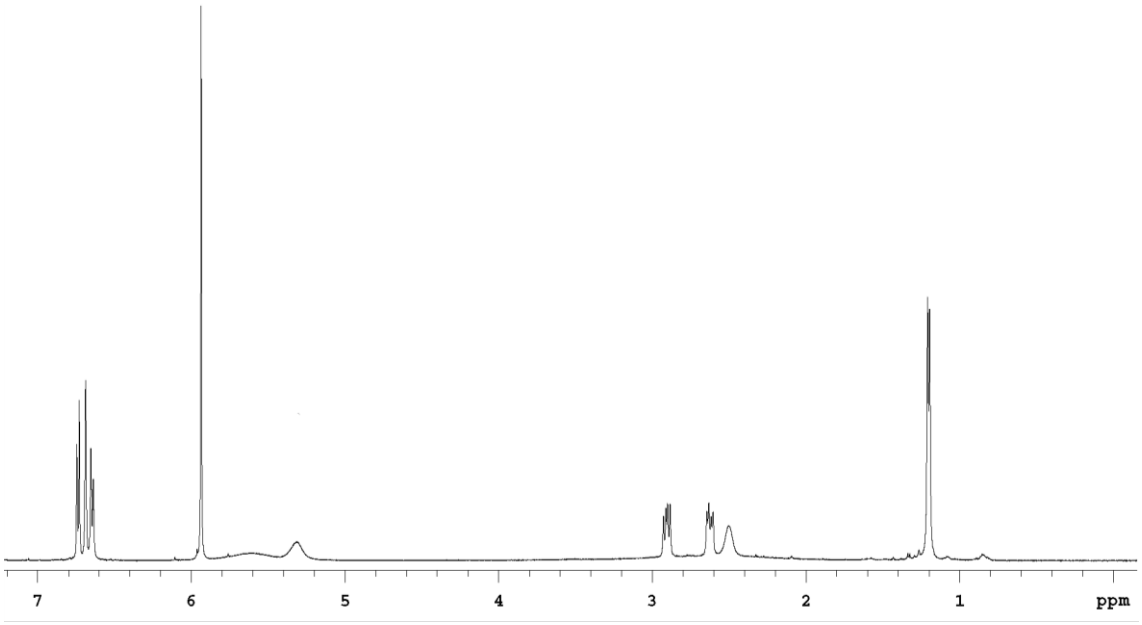


Figure B 3: ^{1}H NMR spectra of MMDPPA

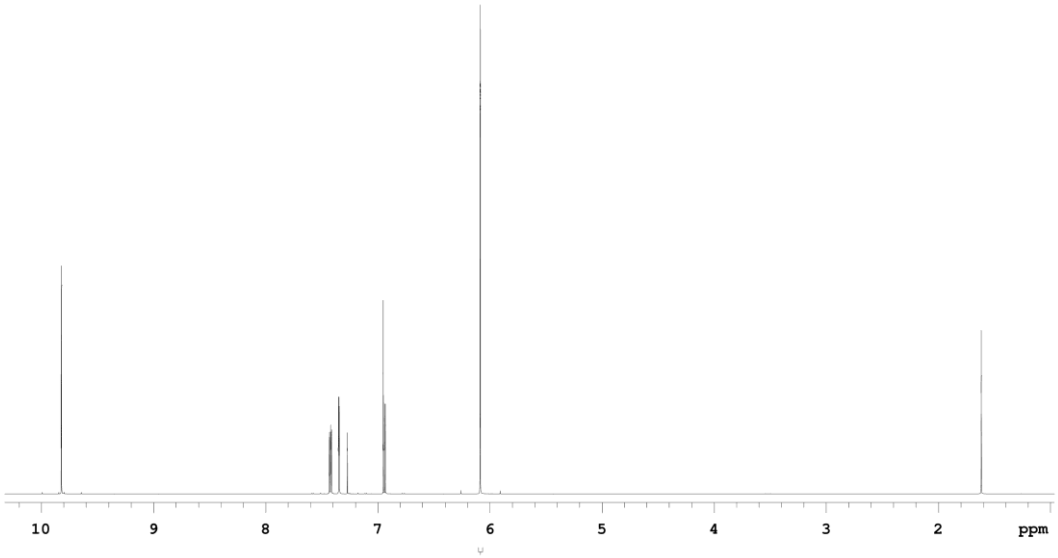


Figure B 4: ^{1}H NMR spectra of piperonal precursor starting material.

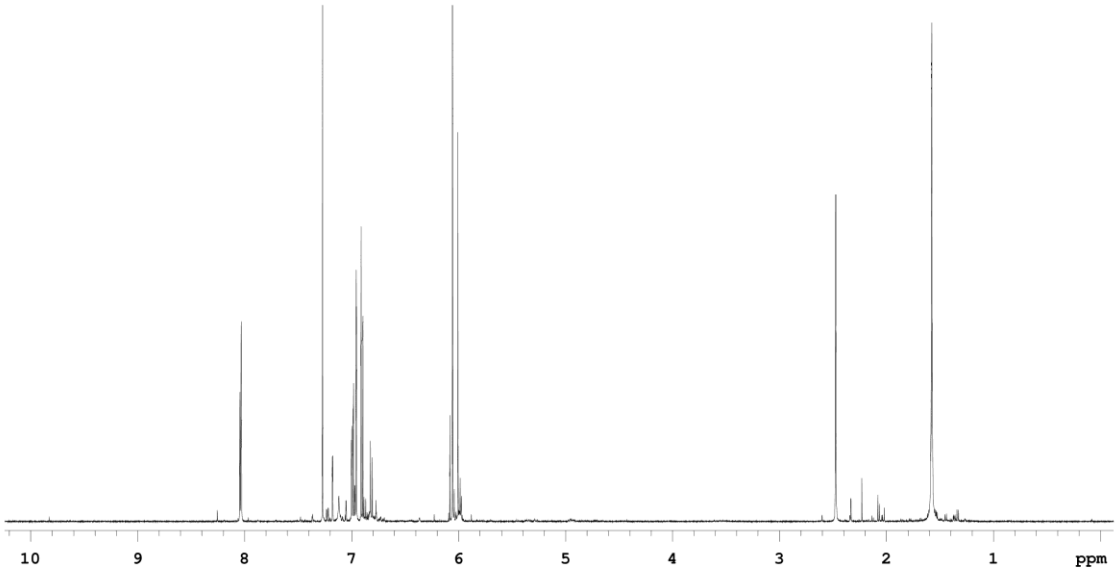


Figure B 5: ^{1}H NMR spectra of 5-(2-nitro-propenyl)-benzo[1,3]dioxole

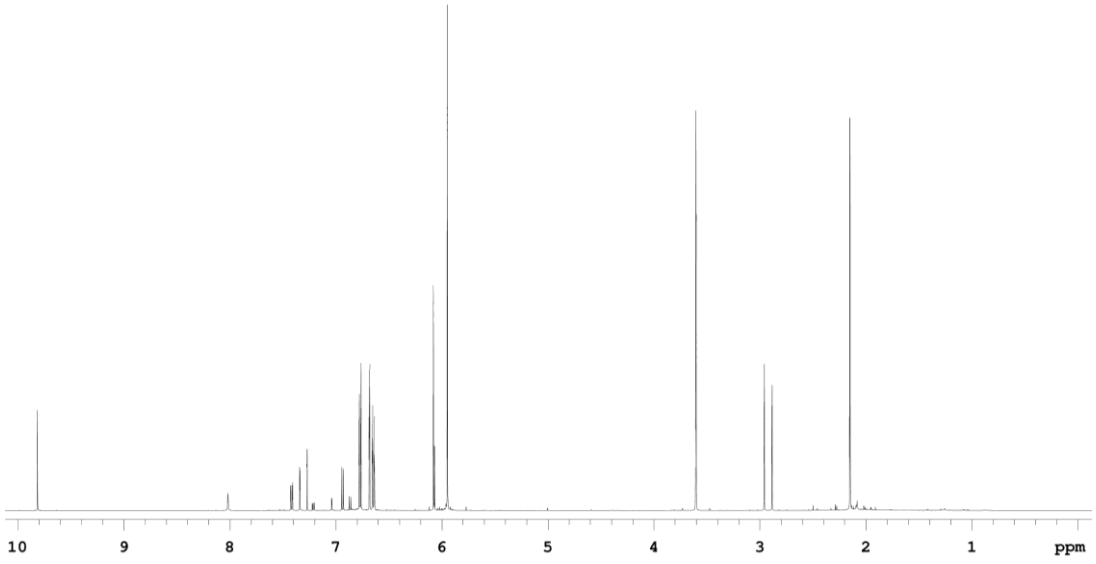


Figure B 6: ^{1}H NMR spectra of MDP2P.

Appendix C- Mass spectrums of the impurities found in 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde oxime

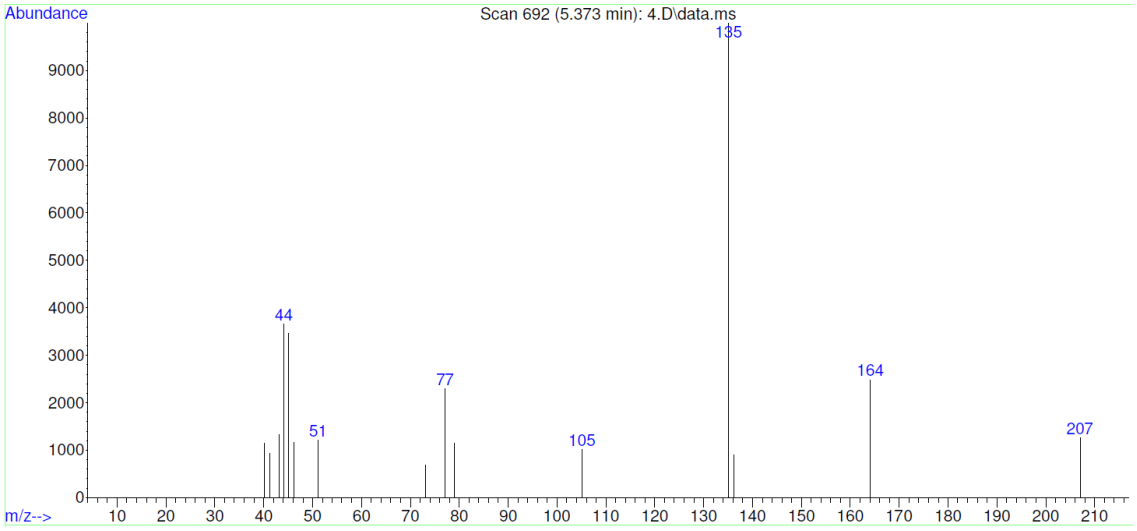


Figure C 1: Mass spectrum of impurity 1

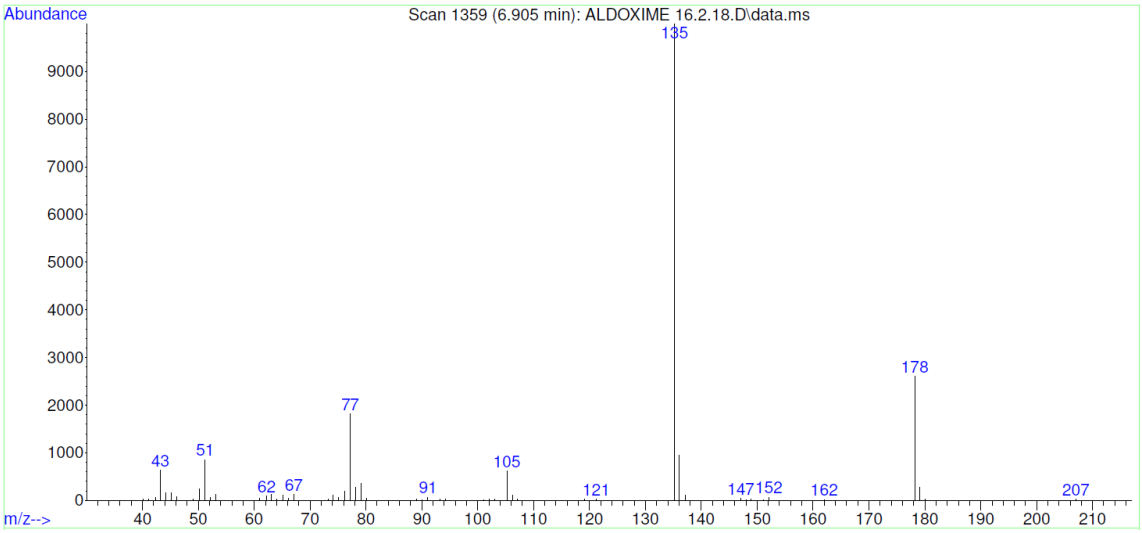


Figure C 2: Mass spectrum of impurity 2

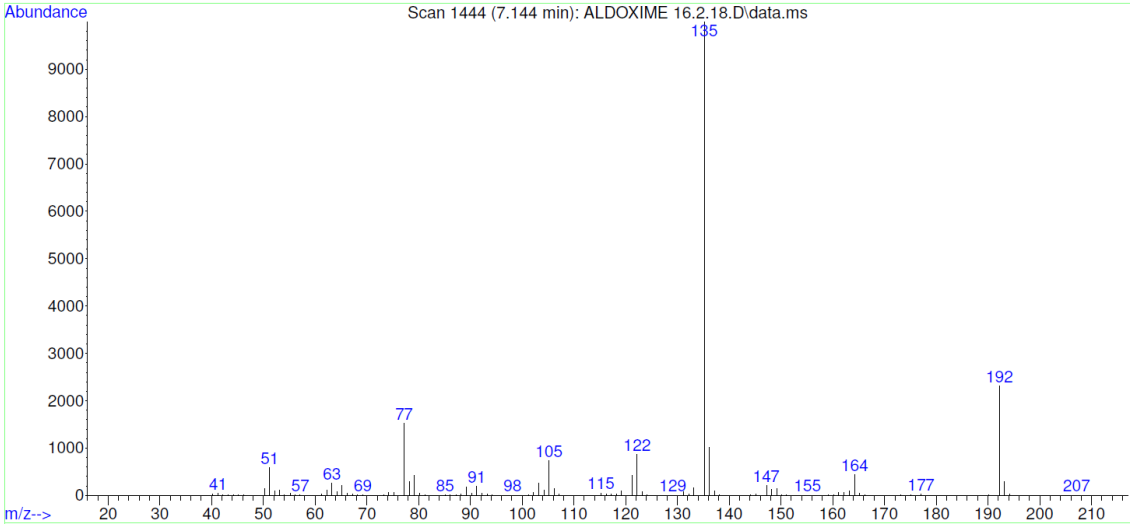


Figure C 3: Mass spectrum for impurity 3

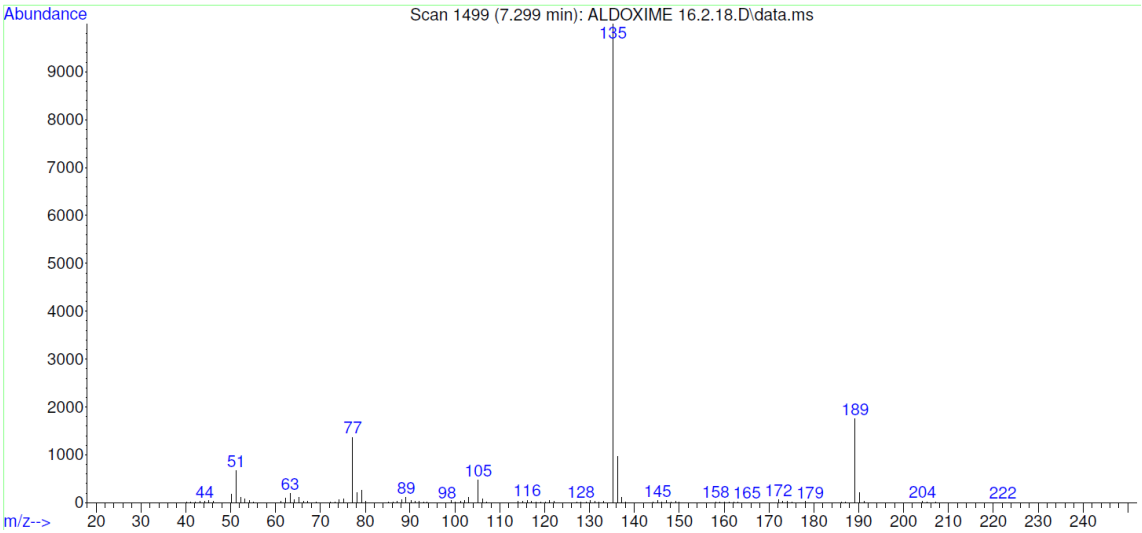


Figure C 4: Mass spectrum for impurity 4

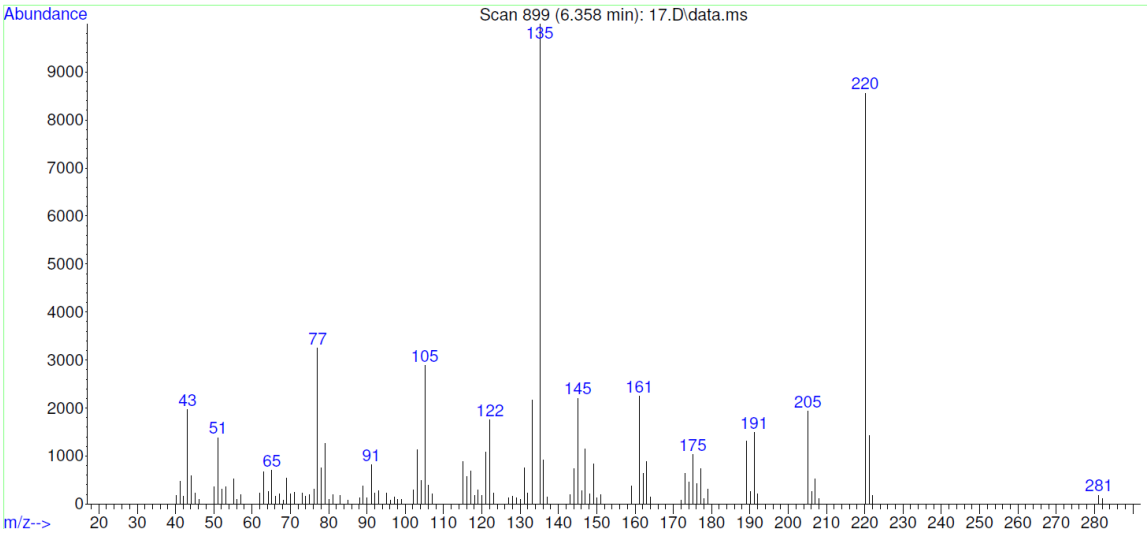


Figure C 5: Mass spectrum for impurity 5

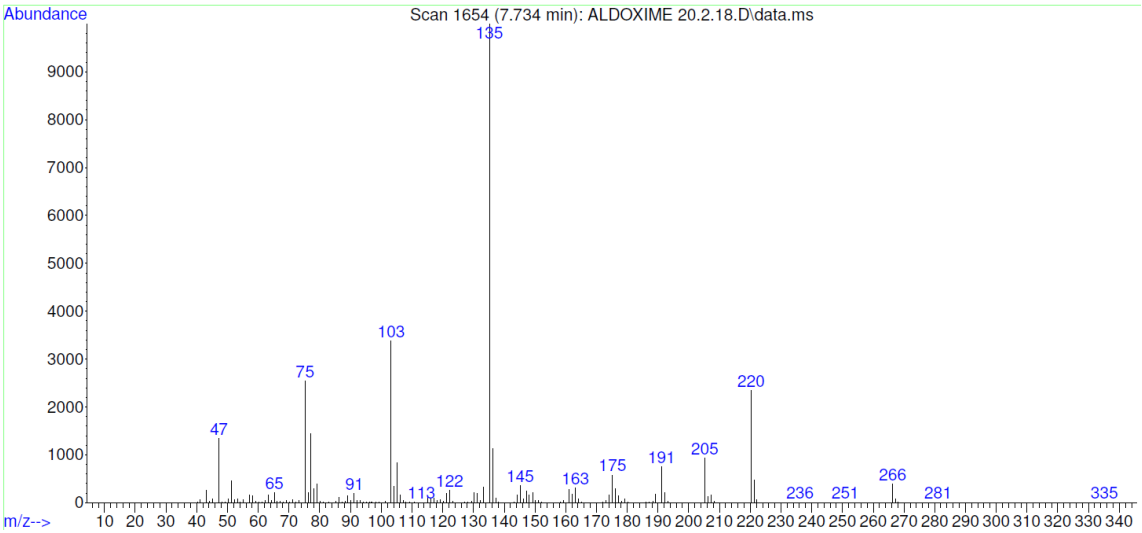


Figure C 6: Mass spectrum for impurity 6

Appendix D- Mass spectrums of the impurities found in 3-Benzo[1,3]dioxol-5-yl-2-methyl-propionamide

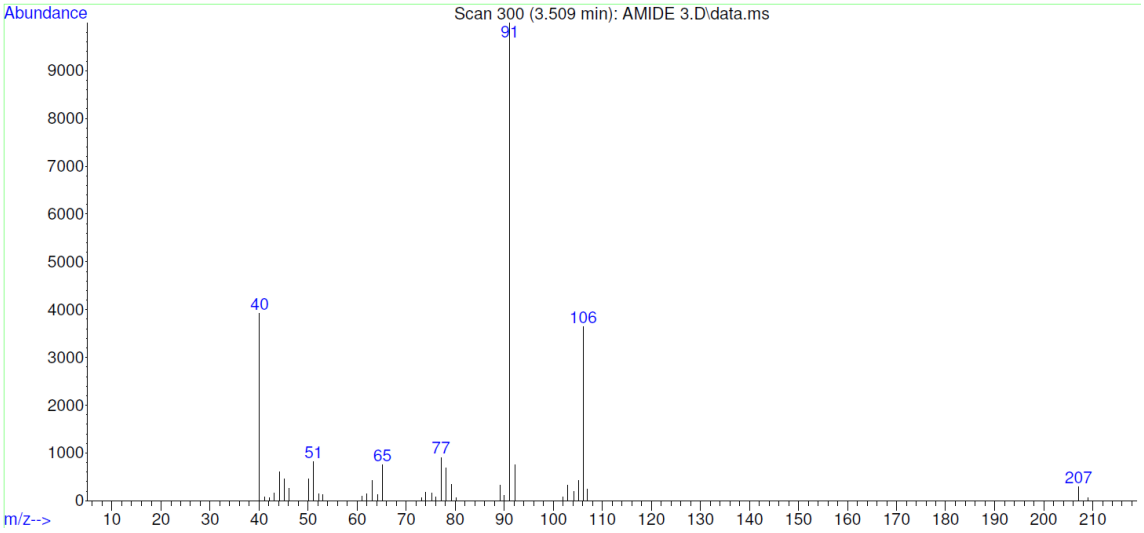


Figure D 1: Mass spectrum of impurity 1

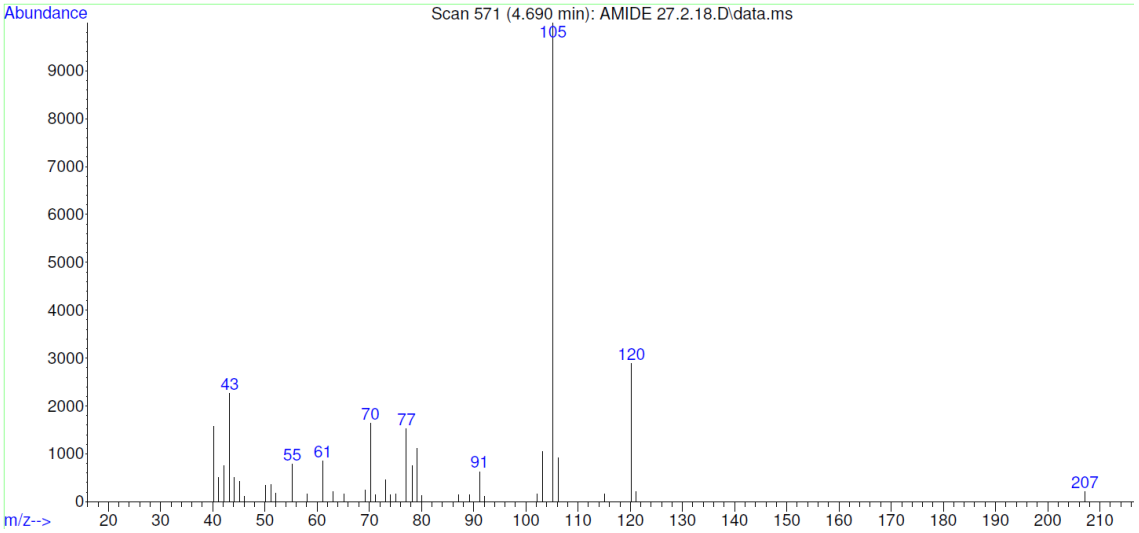


Figure D 2: Mass spectrum of impurity 2

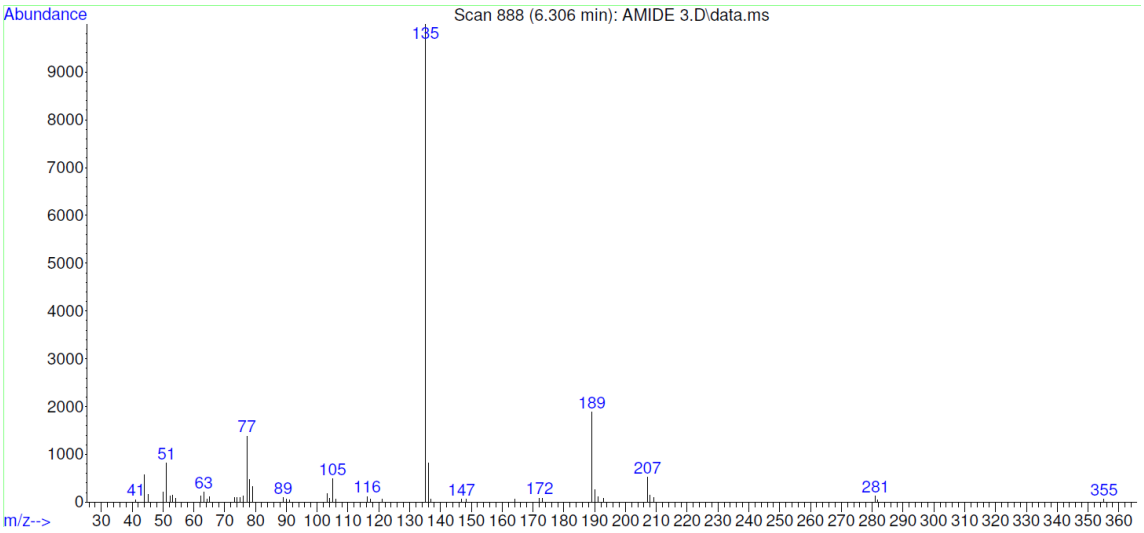


Figure D 3: Mass spectrum for impurity 3

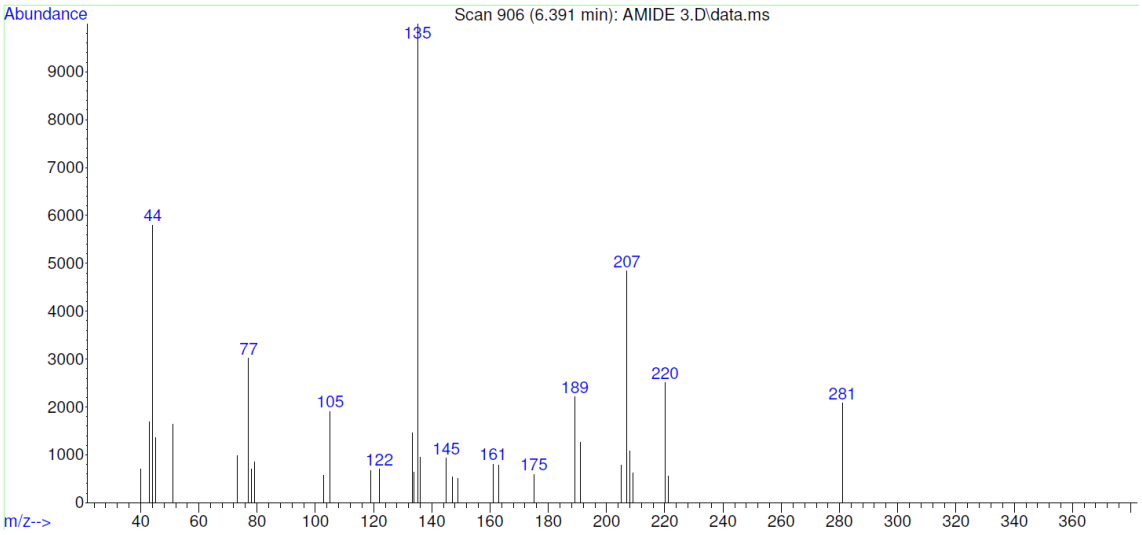


Figure D 4: Mass spectrum of impurity 4

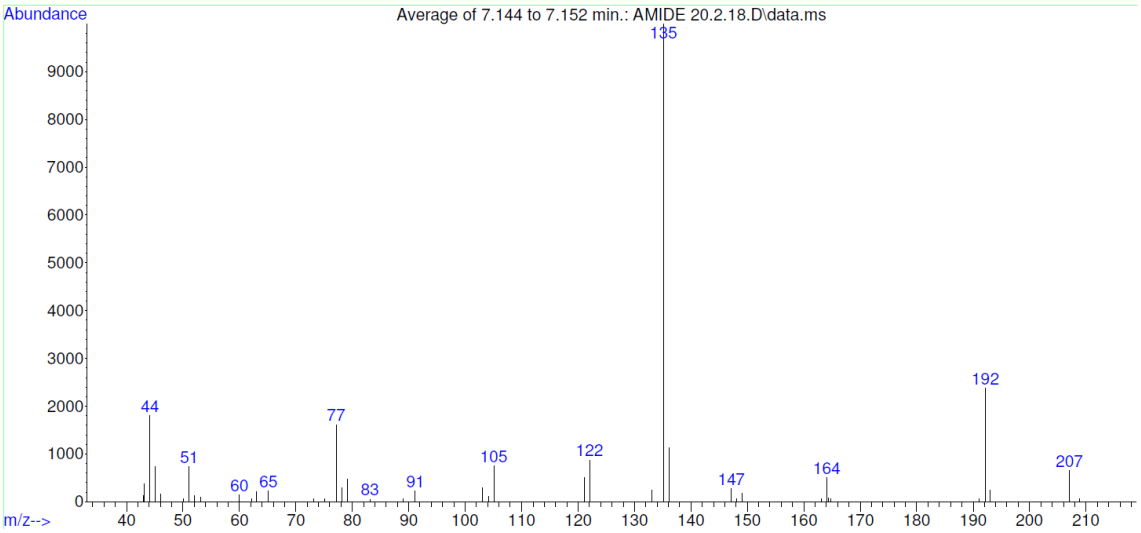


Figure D 5: Mass spectrum for impurity 5

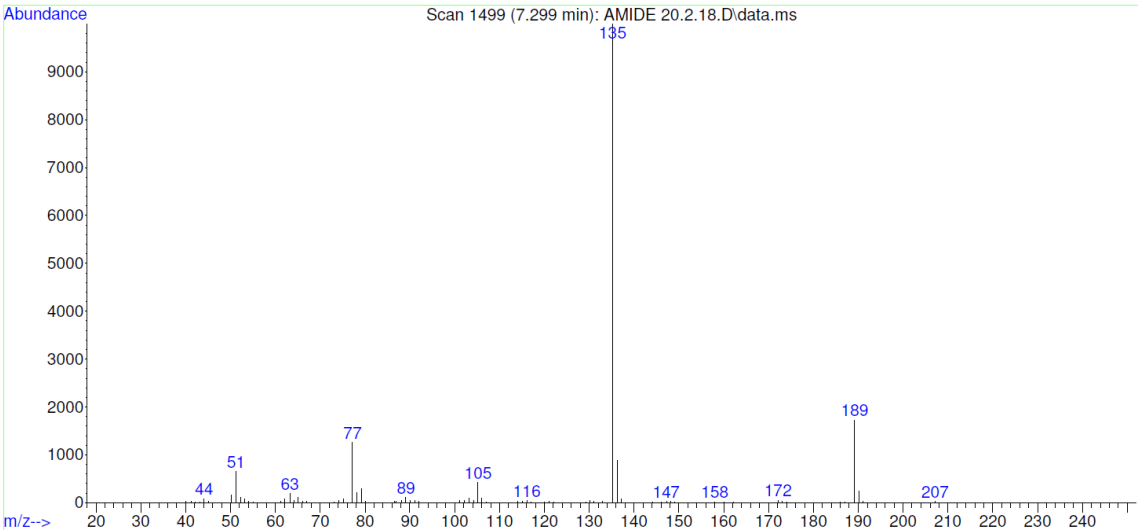


Figure D 6: Mass spectrum for impurity 6

Appendix E- Mass spectrums of the impurities found in MDA synthesized from Helional

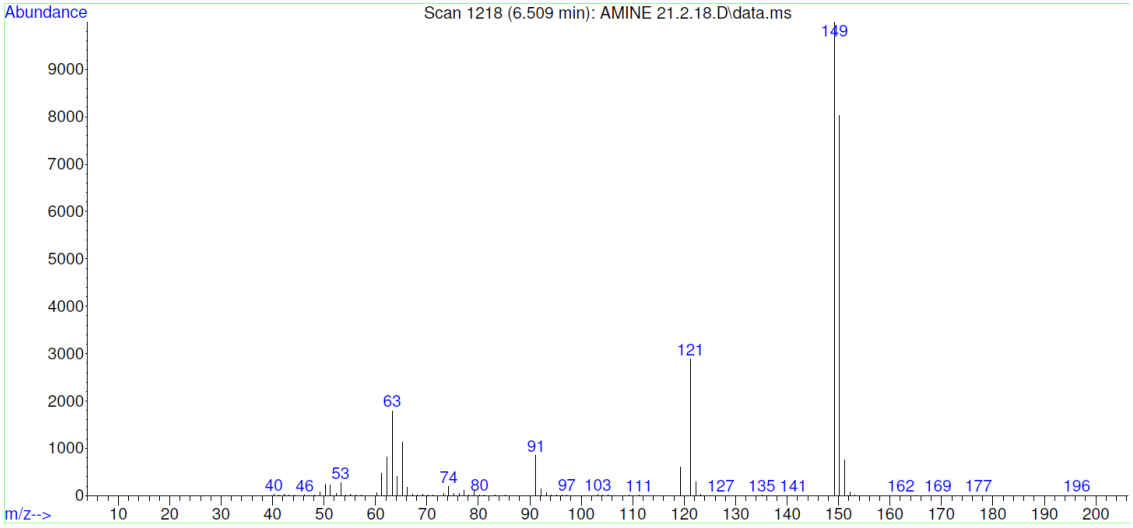


Figure E 1: Mass spectrum for impurity 1

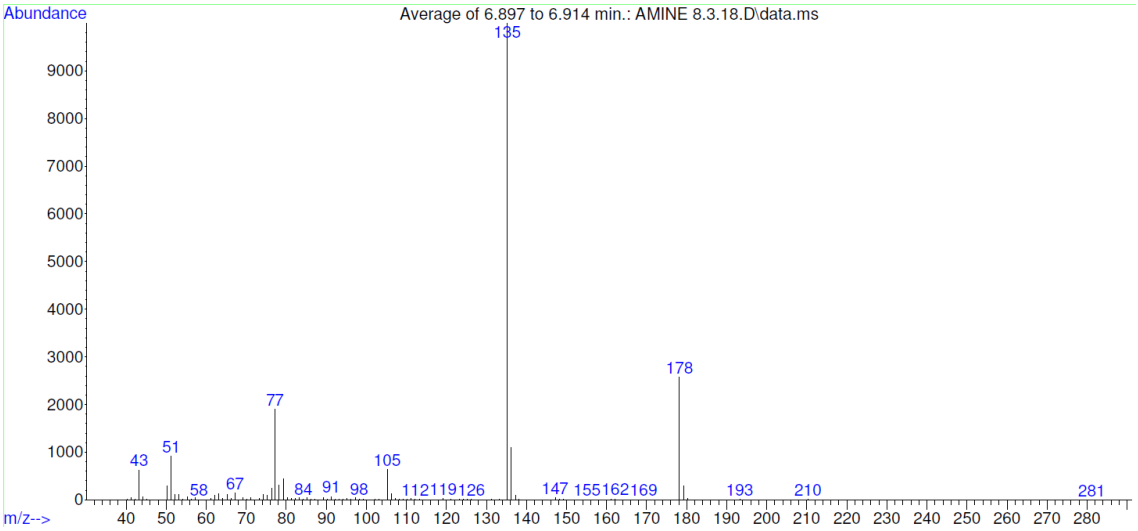


Figure E 2: Mass spectrum for impurity 2

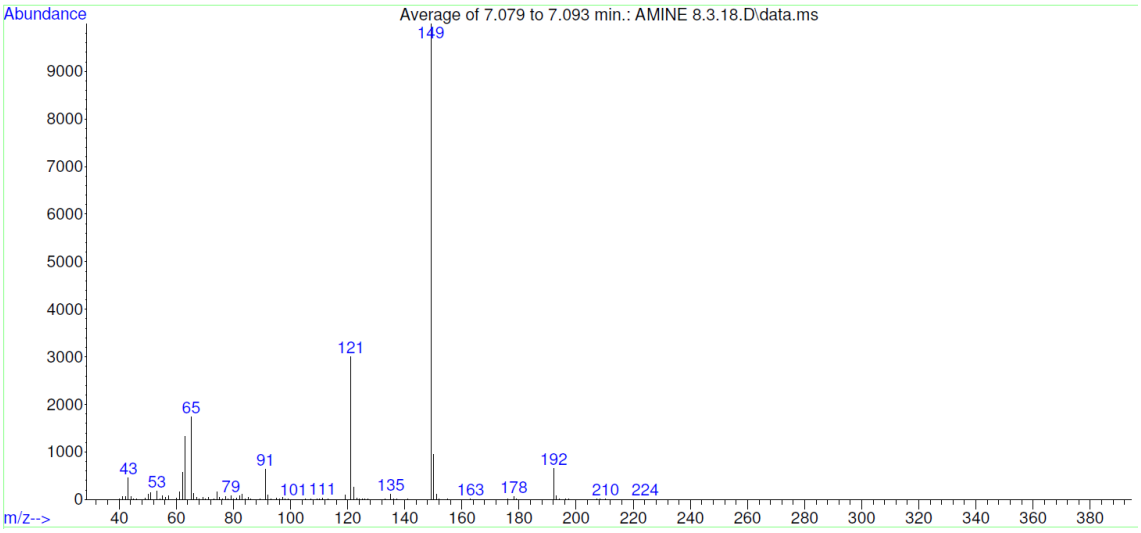


Figure E 3: Mass spectrum for impurity 3

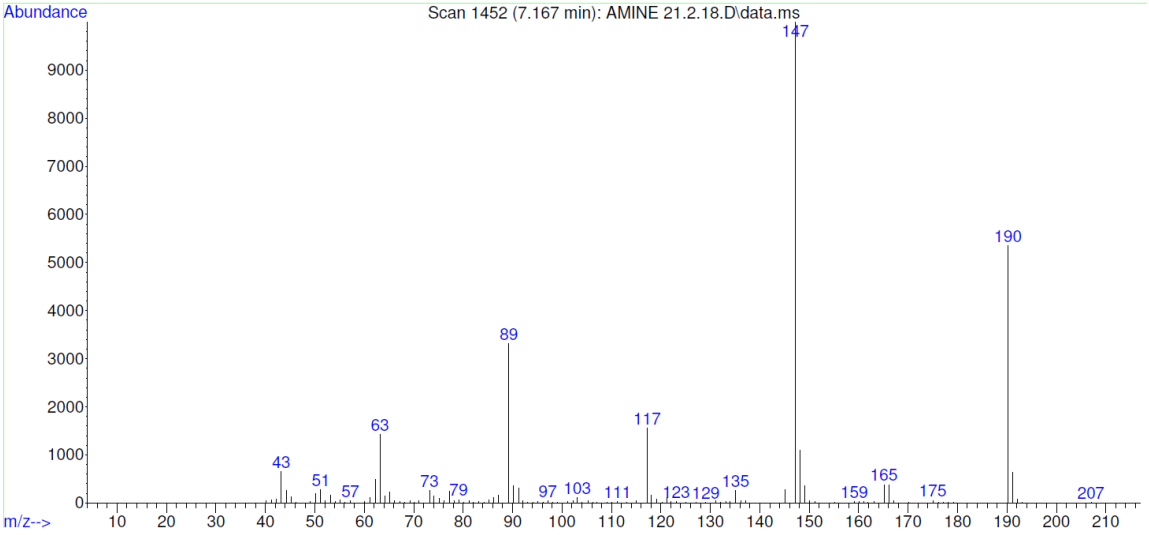


Figure E 4: Mass spectrum for impurity 4

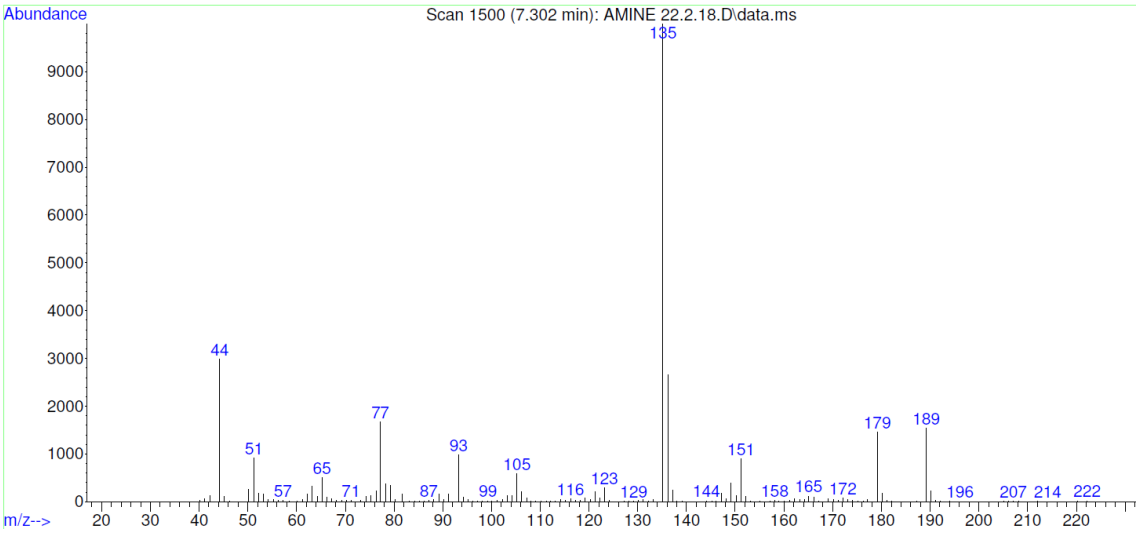


Figure E 5: Mass spectrum for impurity 5

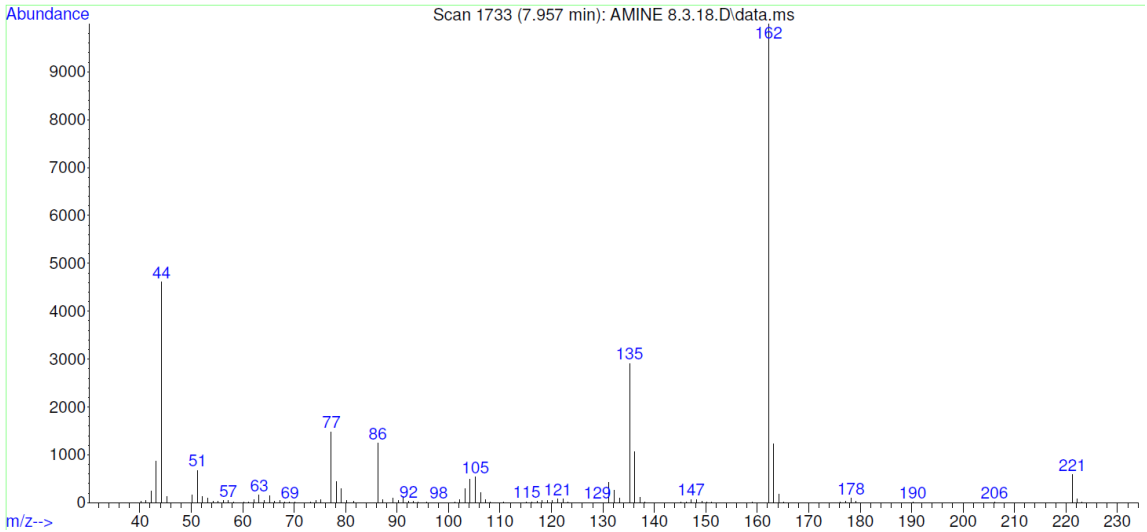


Figure E 6: Mass spectrum for impurity 6

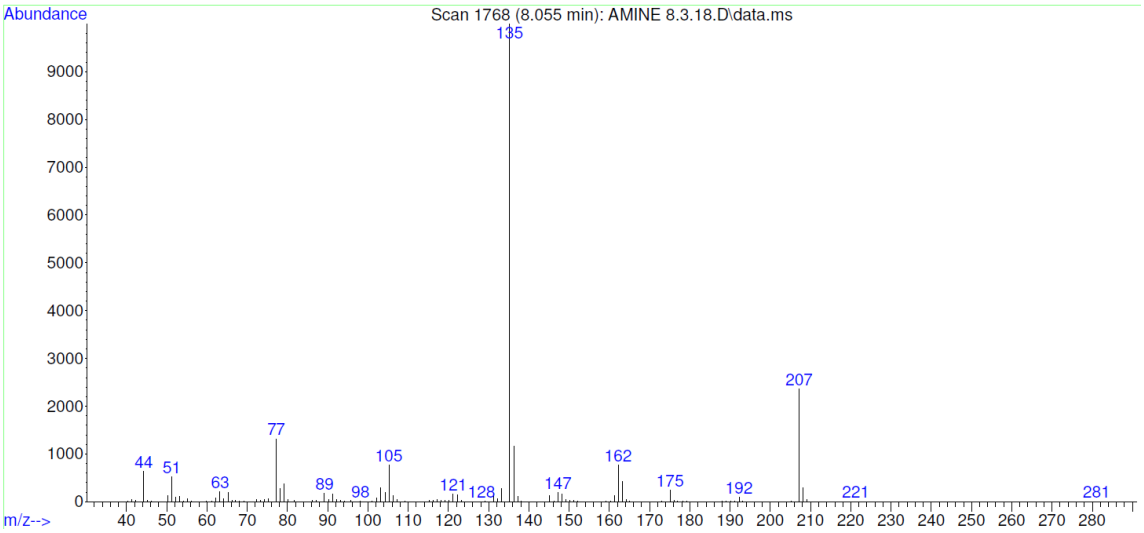


Figure E 7: Mass spectrum for impurity 7

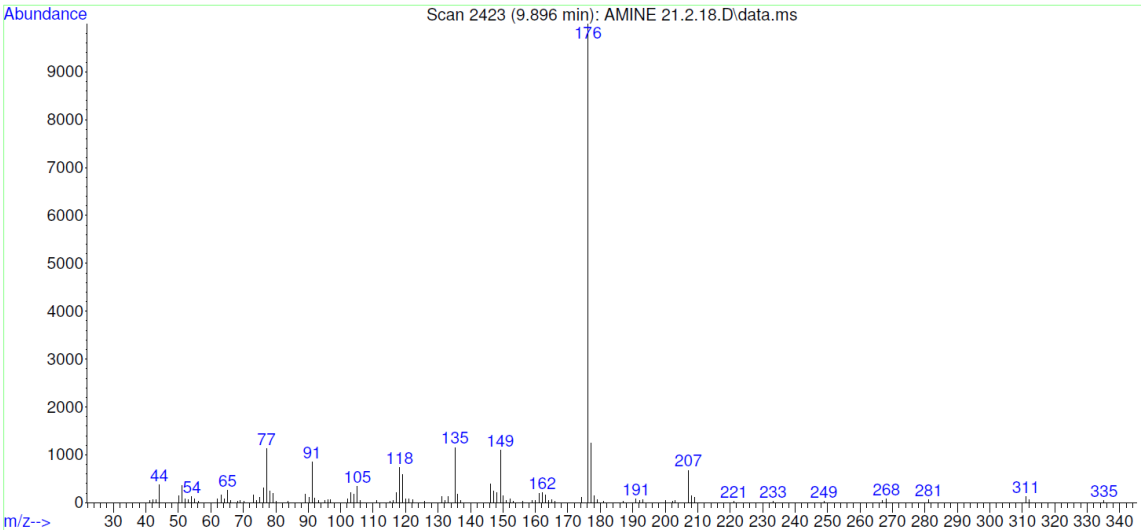


Figure E 8: Mass spectrum for impurity 8

Appendix F- Mass spectrums of the impurities found in 5-(2-nitro-propenyl)benzo[1,3]dioxole

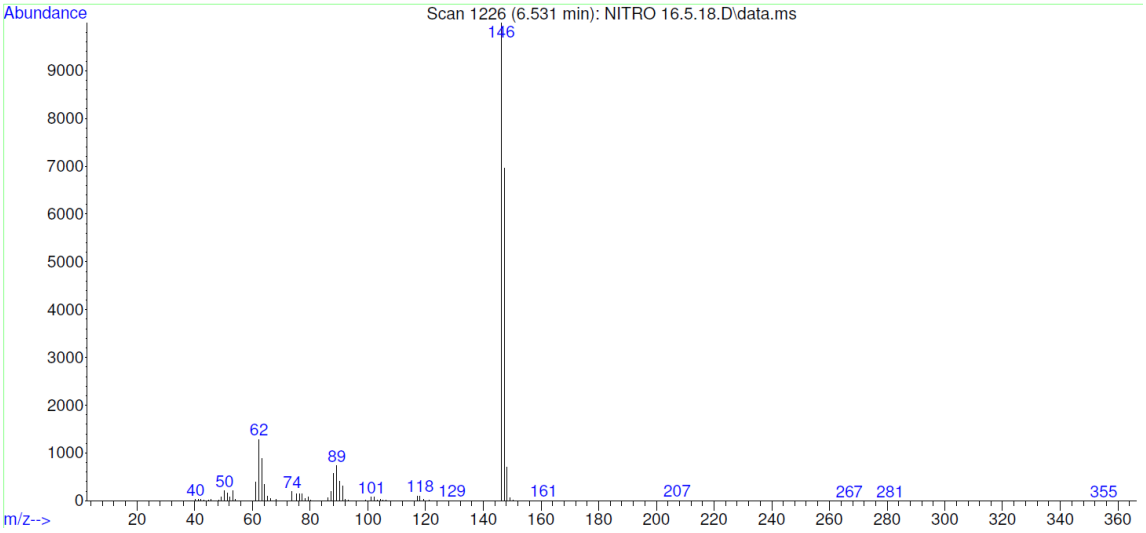


Figure F 1: Mass spectrum for impurity 1

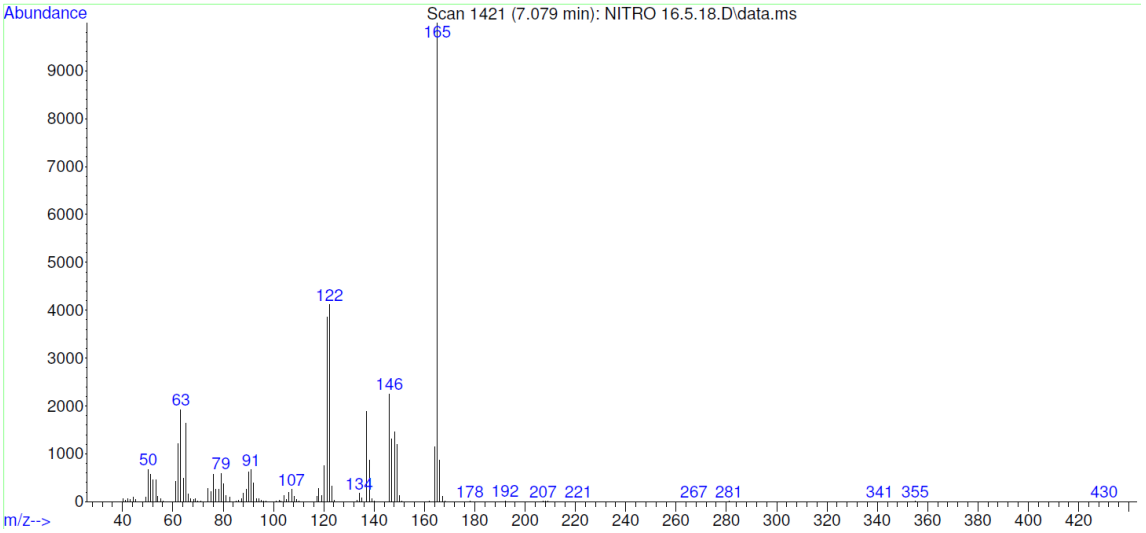


Figure F 2: Mass spectrum for impurity 2

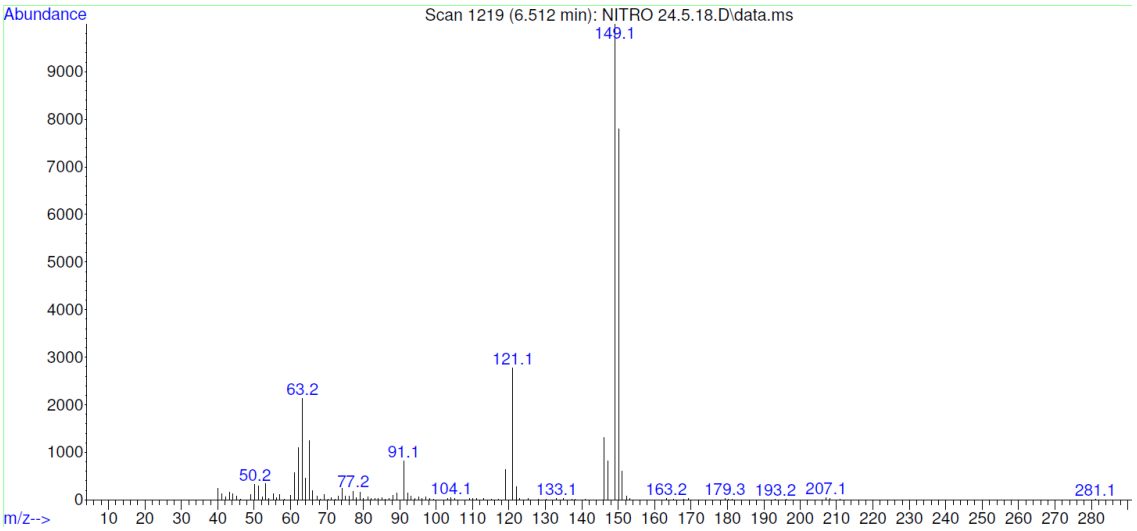


Figure F 3: Mass spectrum for impurity 3

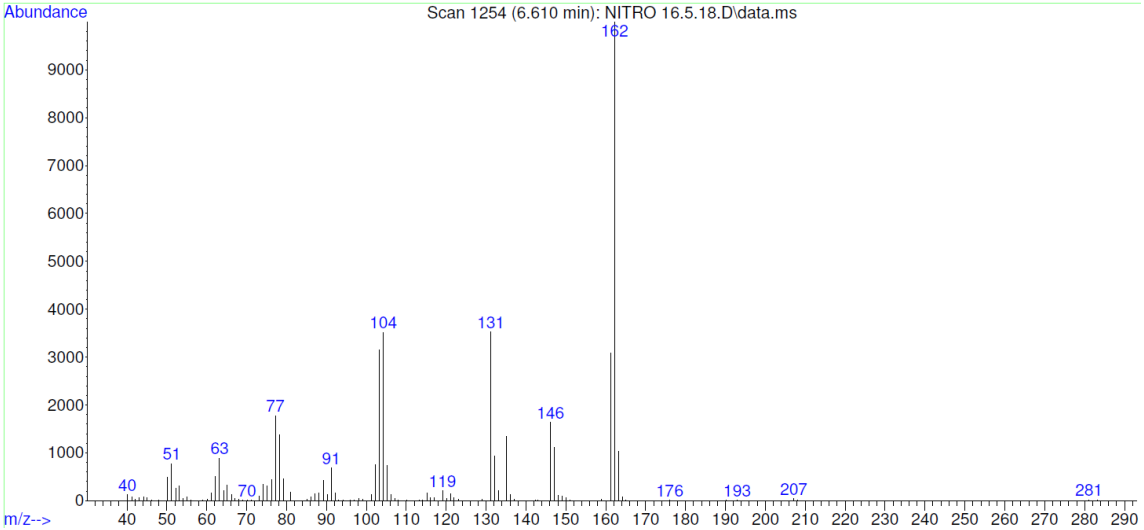


Figure F 4: Mass spectrum for impurity 4

Appendix G- Mass spectrums of the impurities found in 1-Benzo[1,3]dioxol-5-yl-propan-2-one

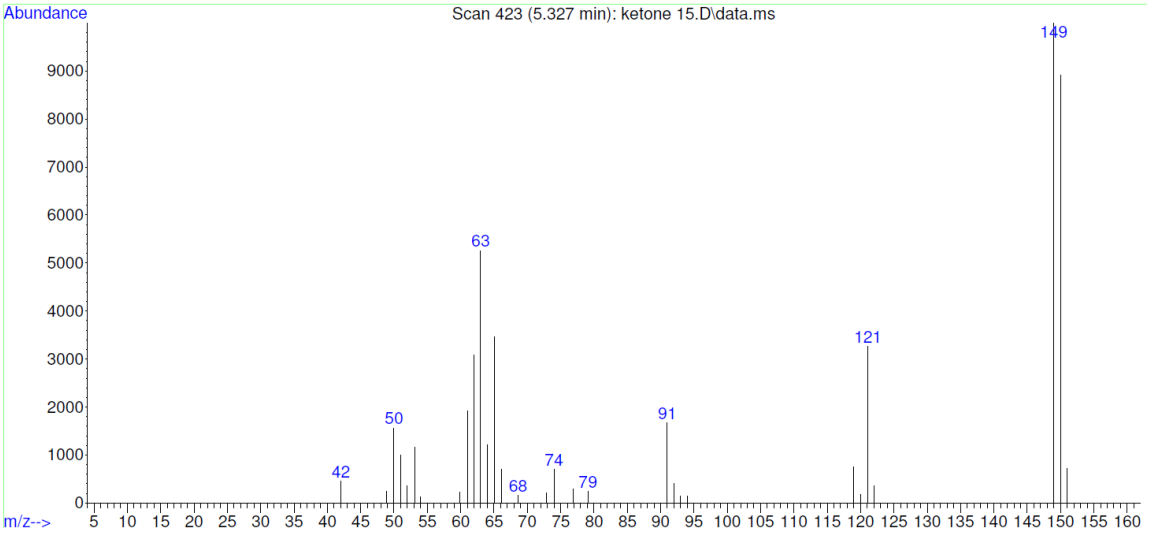


Figure G 1: Mass spectrum for impurity 1

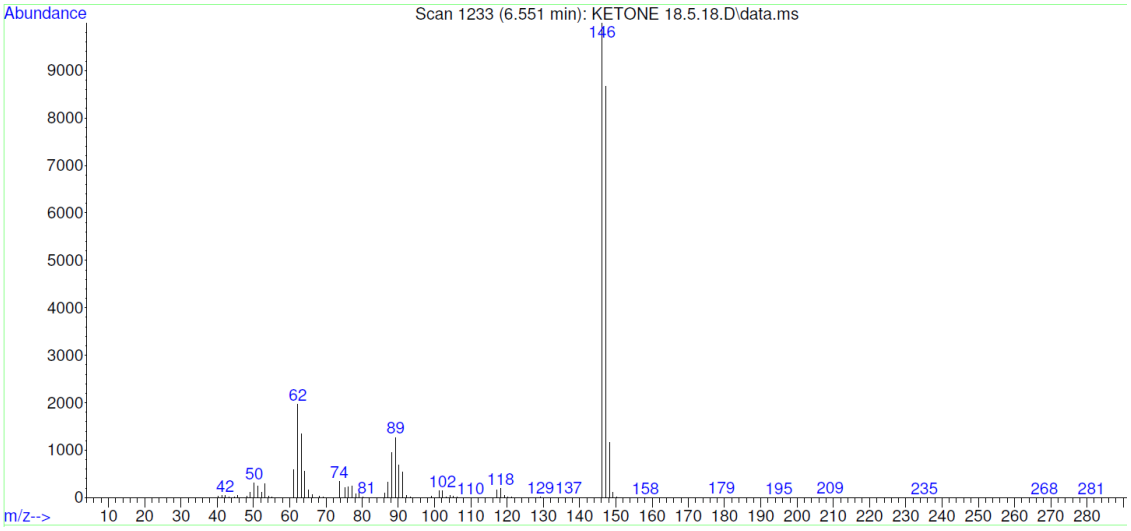


Figure G 2: Mass spectrum for impurity 2

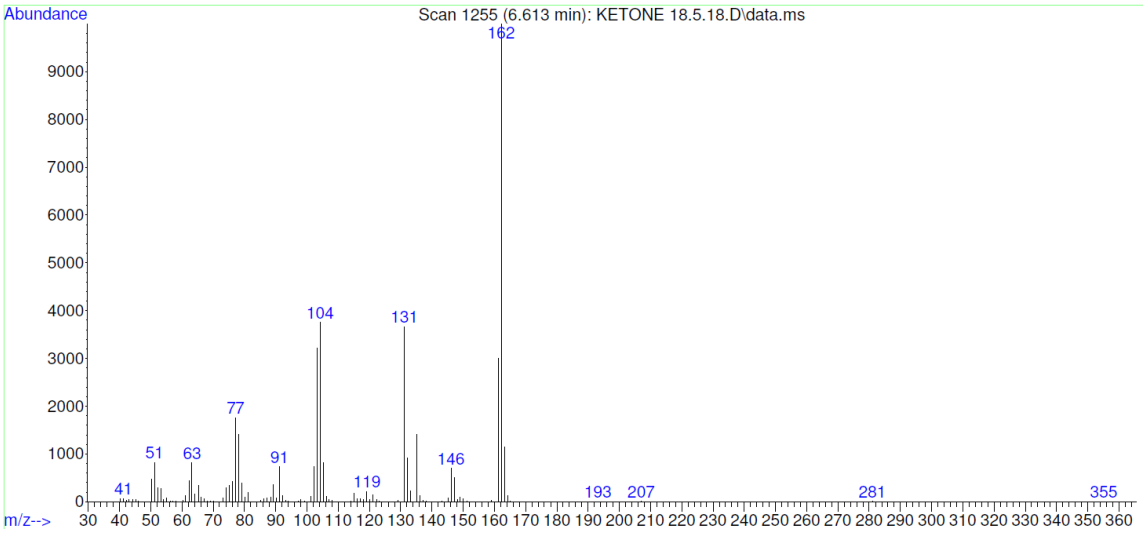


Figure G 3: Mass spectrum for impurity 3

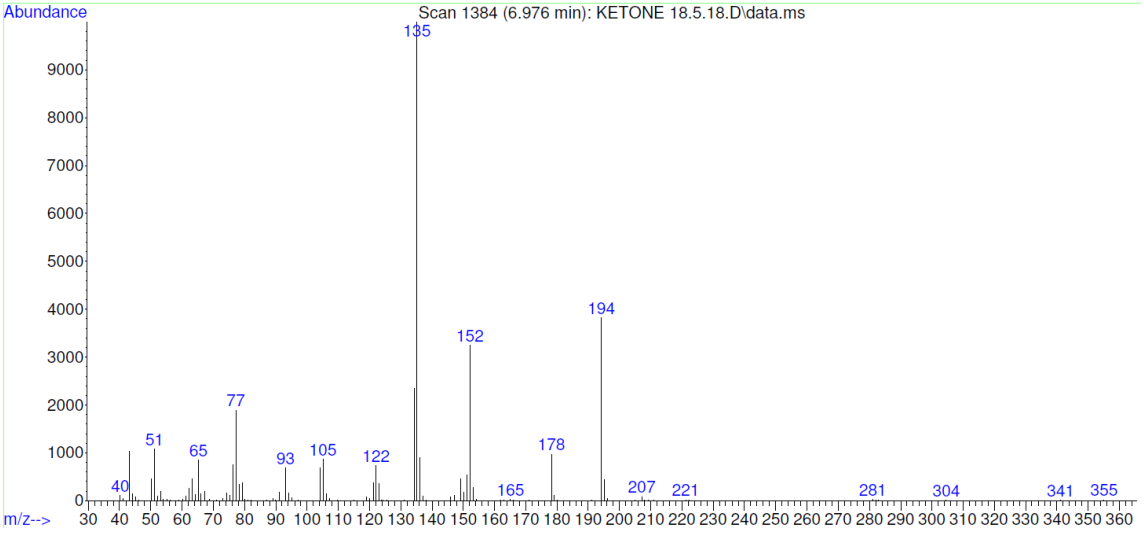


Figure G 4: Mass spectrum for impurity 4

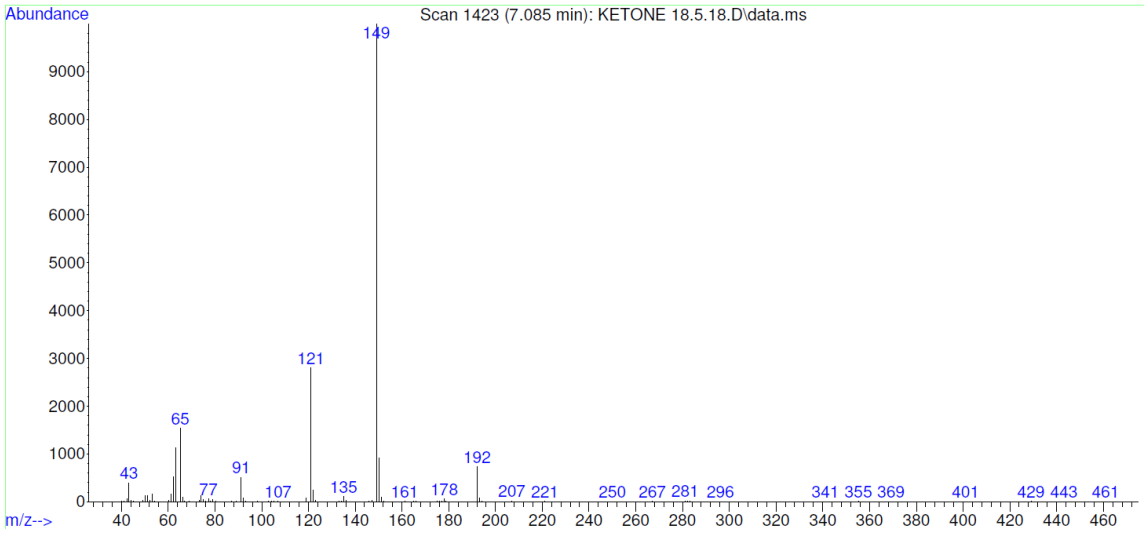


Figure G 5: Mass spectrum for impurity 5

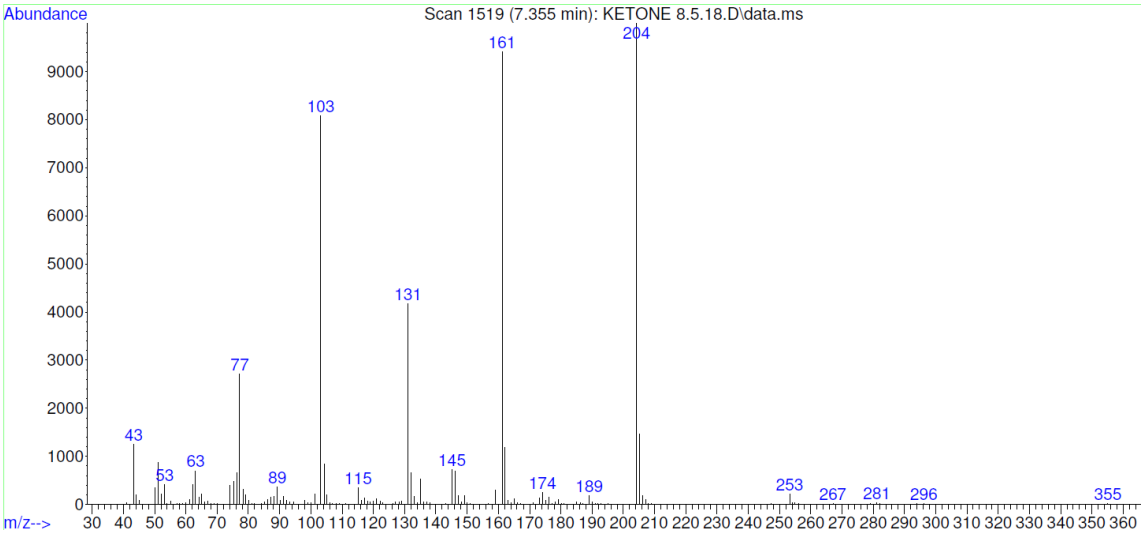


Figure G 6: Mass spectrum for impurity 6

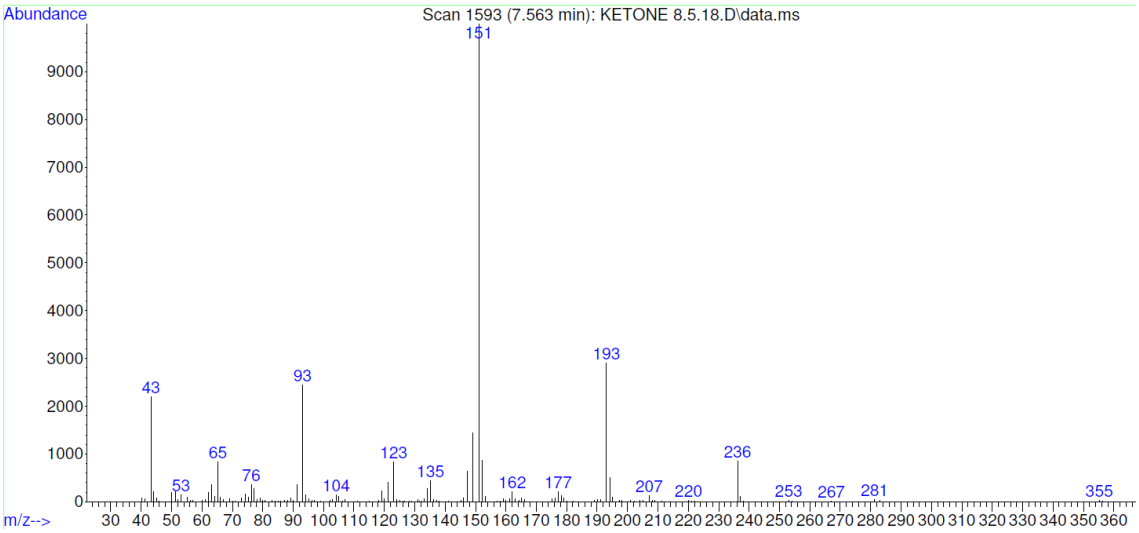


Figure G 7: Mass spectrum for impurity 7

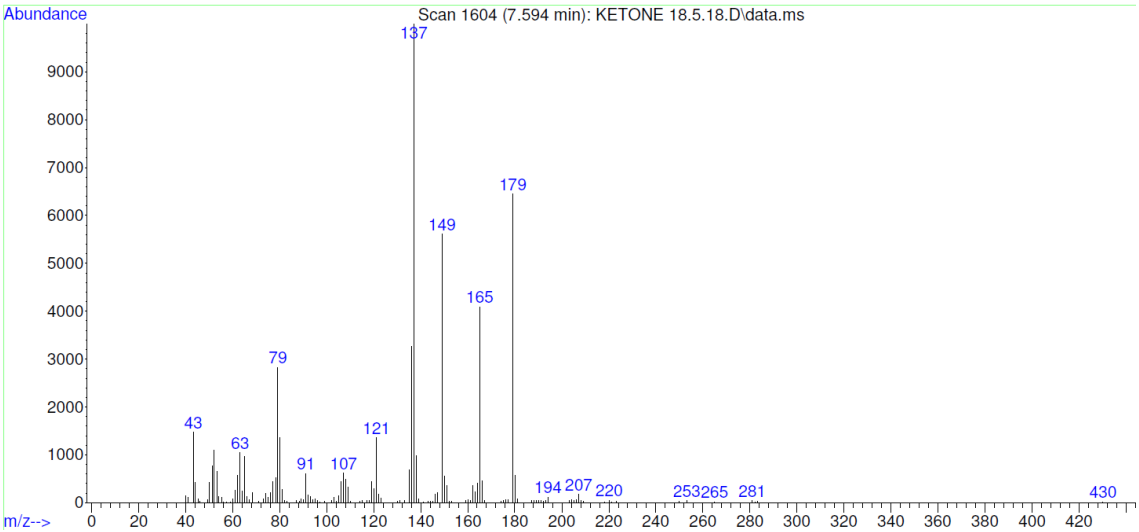


Figure G 8: Mass spectrum for impurity 8

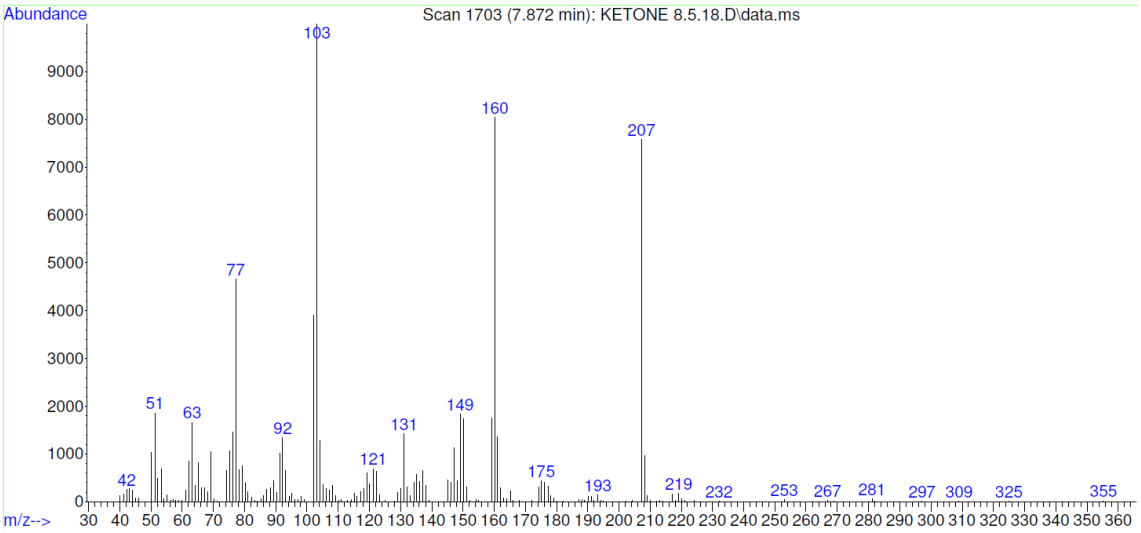


Figure G 9: Mass spectrum for impurity 9

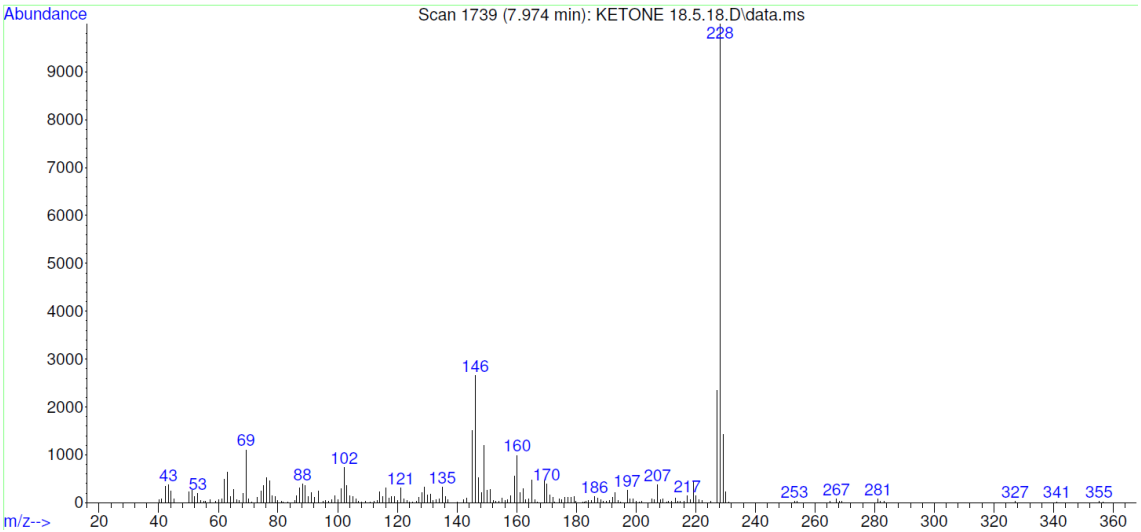


Figure G 10: Mass spectrum for impurity 10

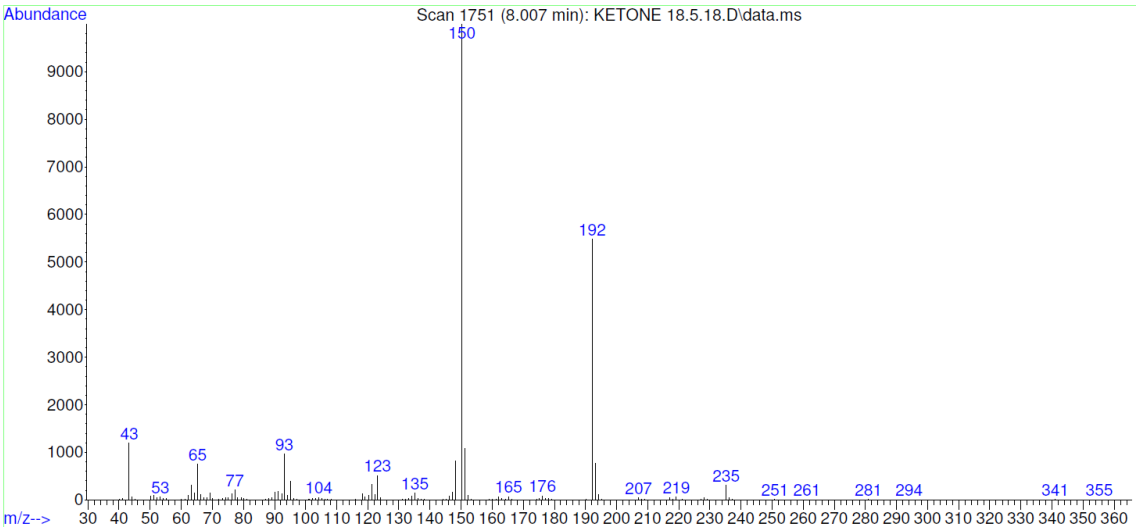


Figure G 11: Mass spectrum for impurity 11

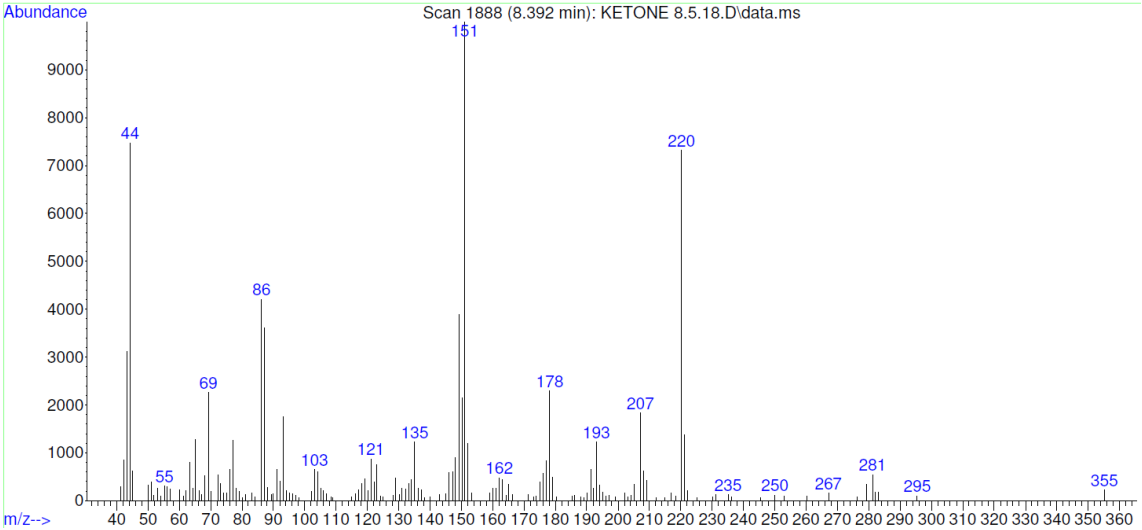


Figure G 12: Mass spectrum for impurity 12

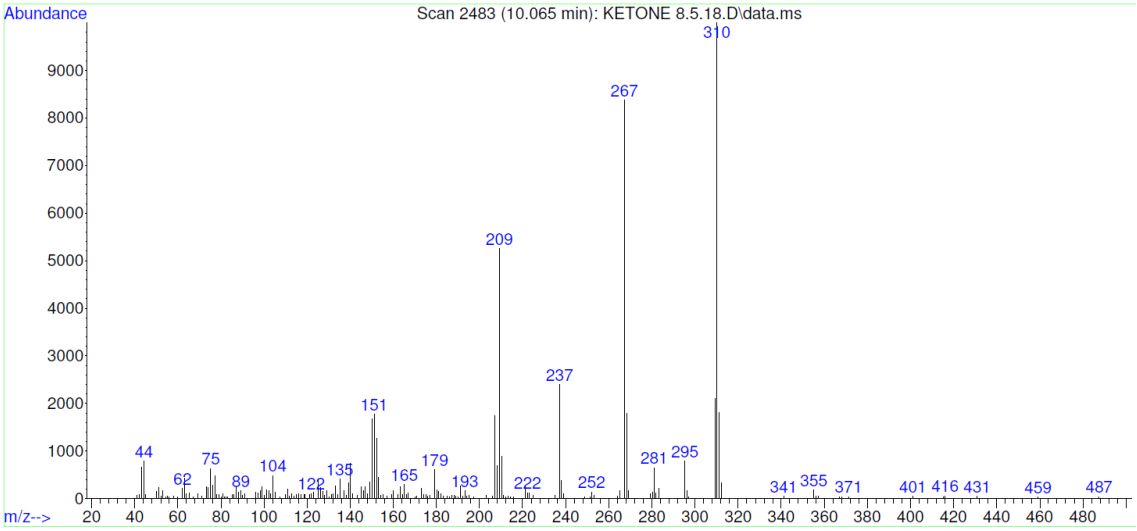


Figure G 13: Mass spectrum for impurity 13

Appendix H- Mass spectrums of the impurities found in MDA synthesized from piperonal

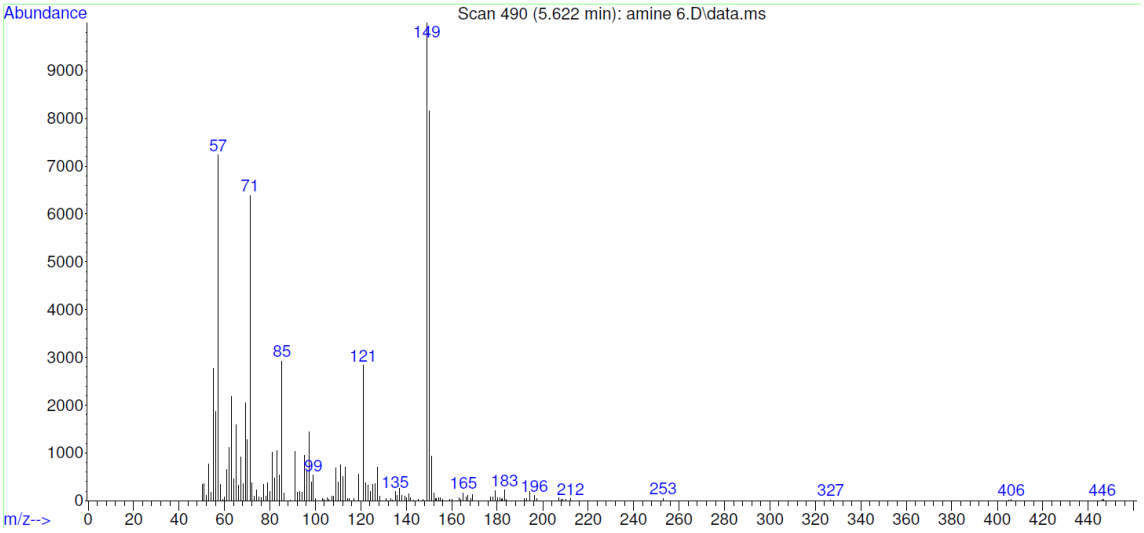


Figure H 1: Mass spectrum for impurity 1

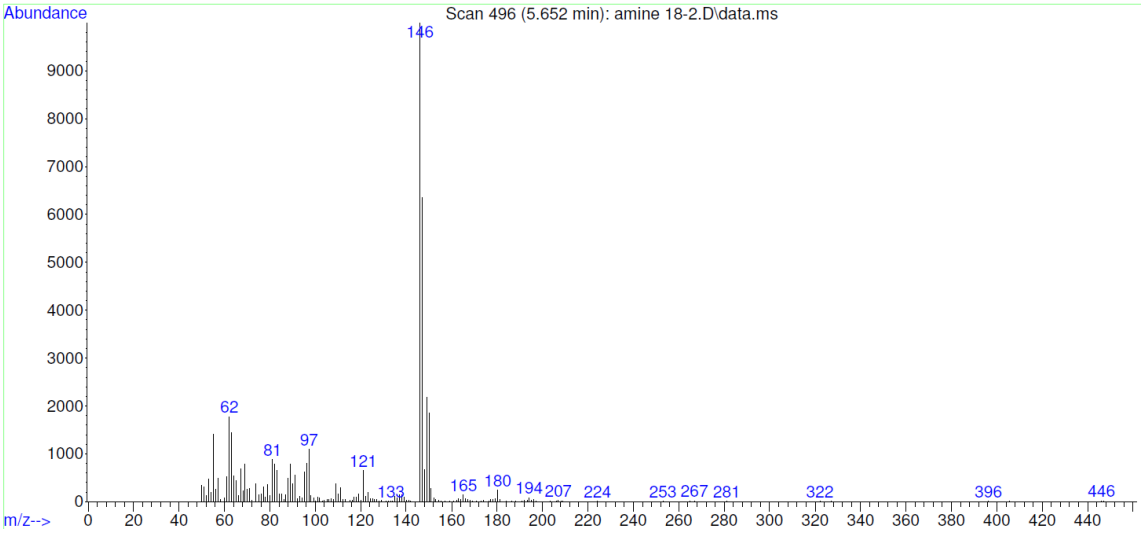


Figure H 2: Mass spectrum for impurity 2

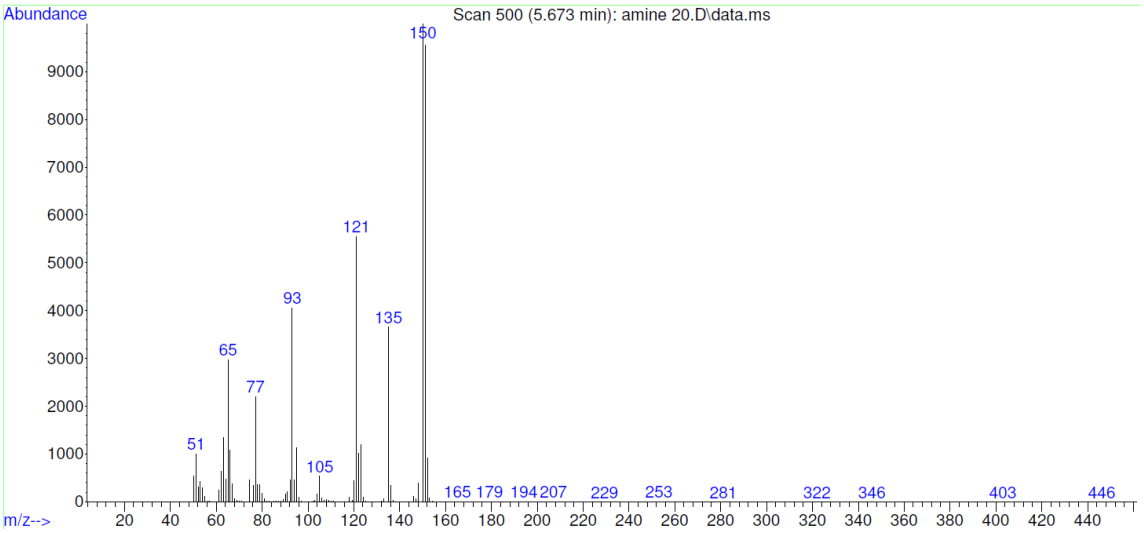


Figure H 3: Mass spectrum for impurity 3

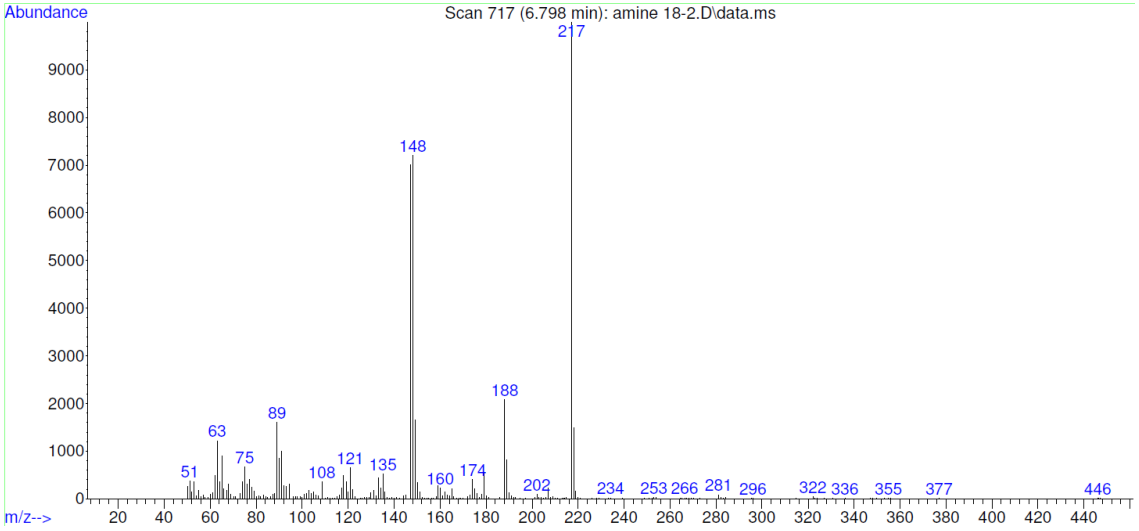


Figure H 4: Mass spectrum for impurity 4

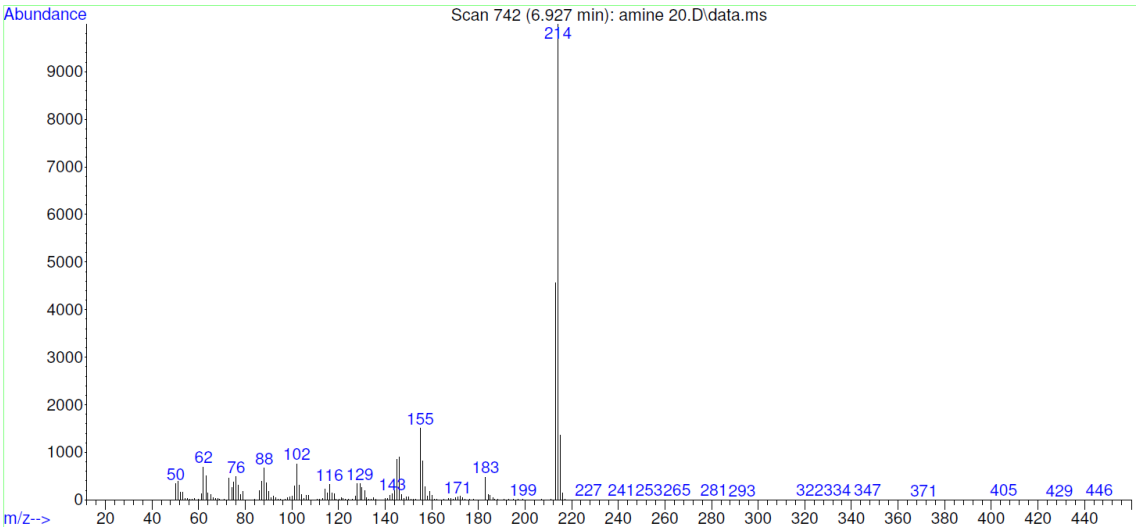


Figure H 5: Mass spectrum for impurity 5

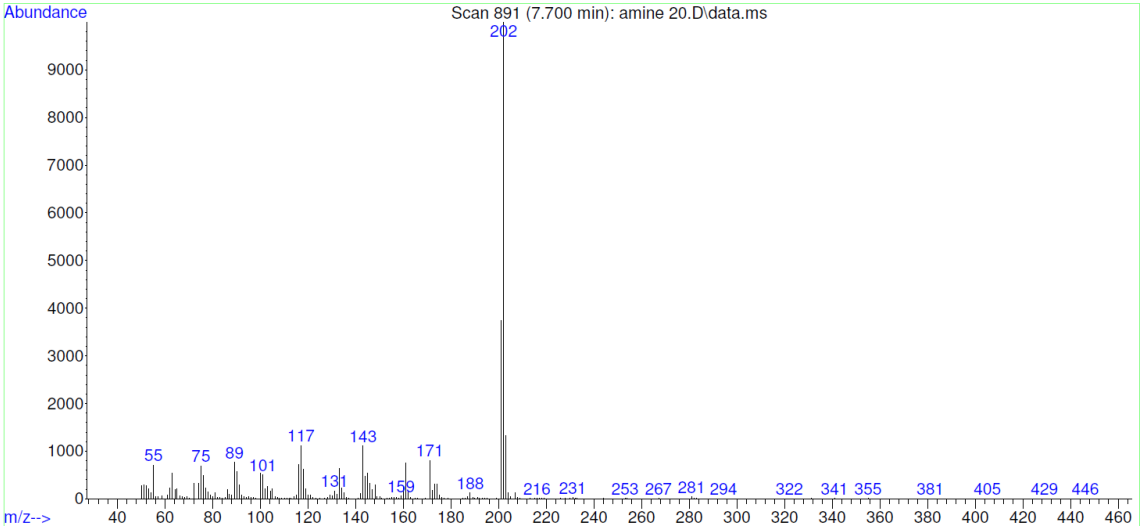


Figure H 6: Mass spectrum for impurity 6

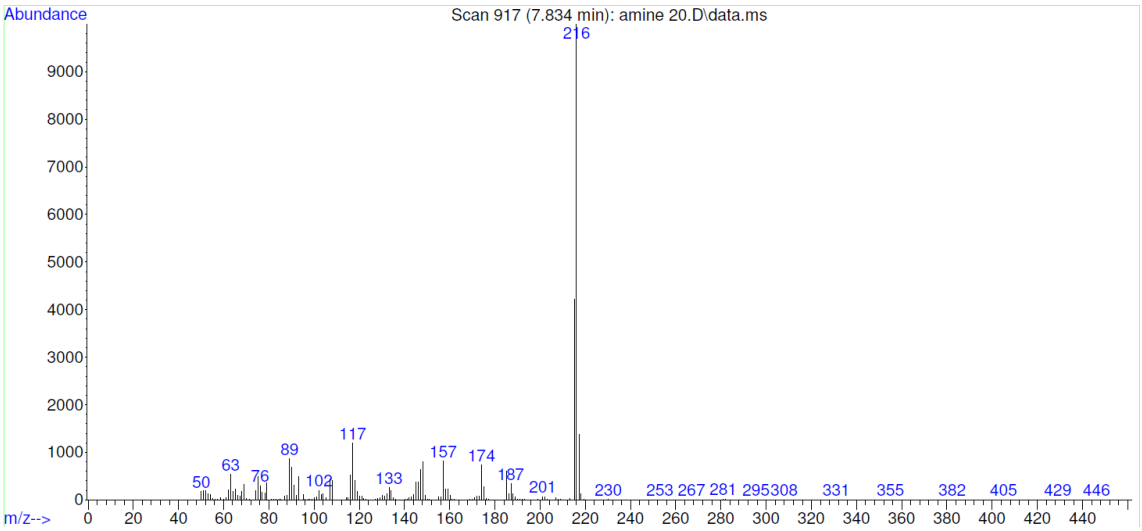


Figure H 7: Mass spectrum for impurity 7

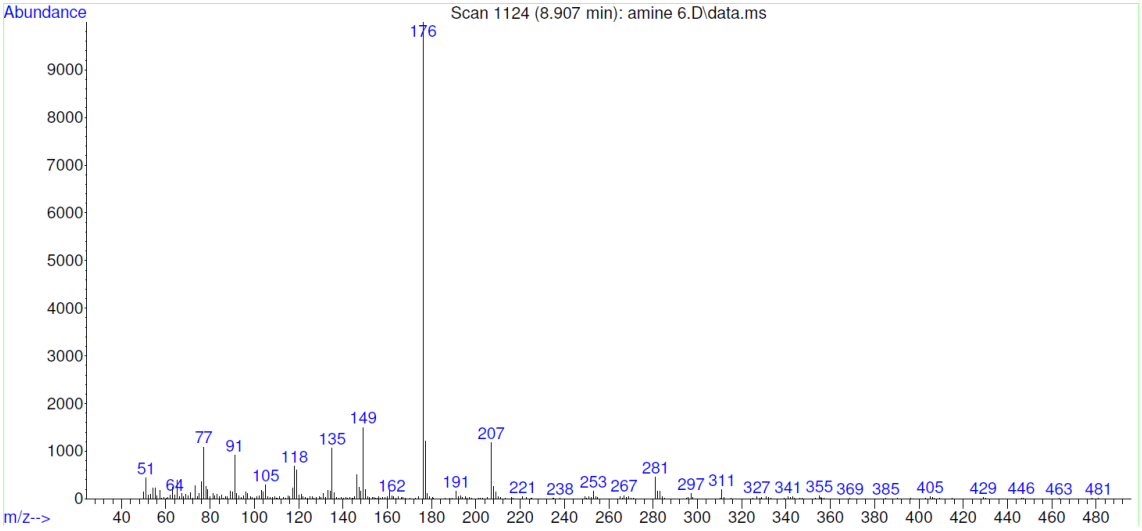


Figure H 8: Mass spectrum for impurity 8

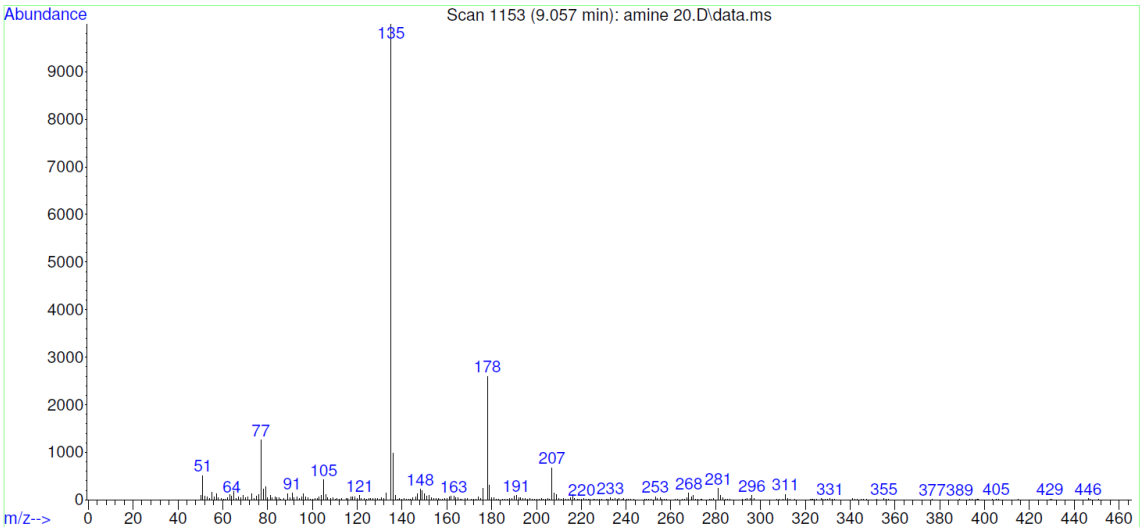


Figure H 9: Mass spectrum for impurity 9

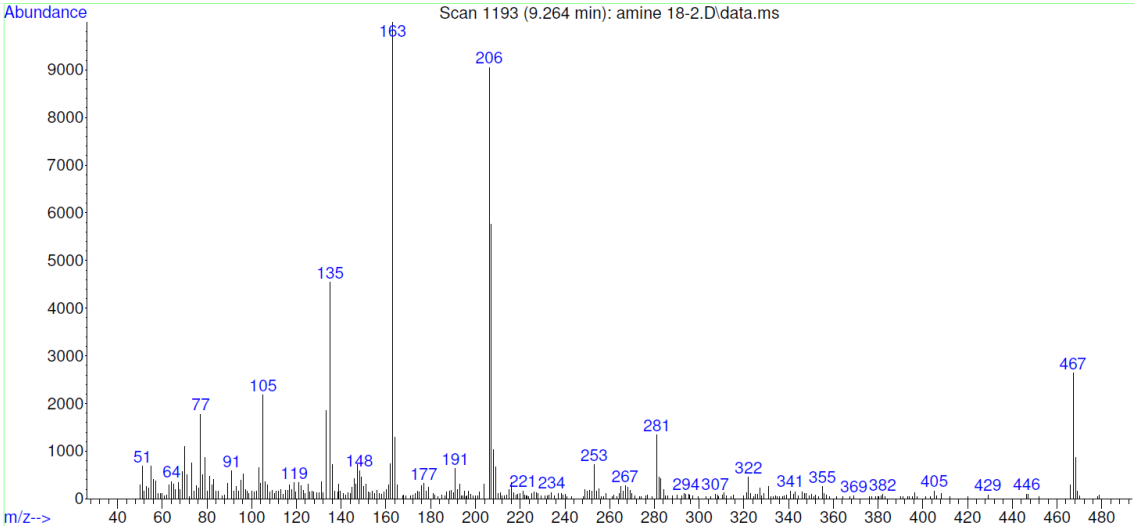


Figure H 10: Mass spectrum for impurity 10

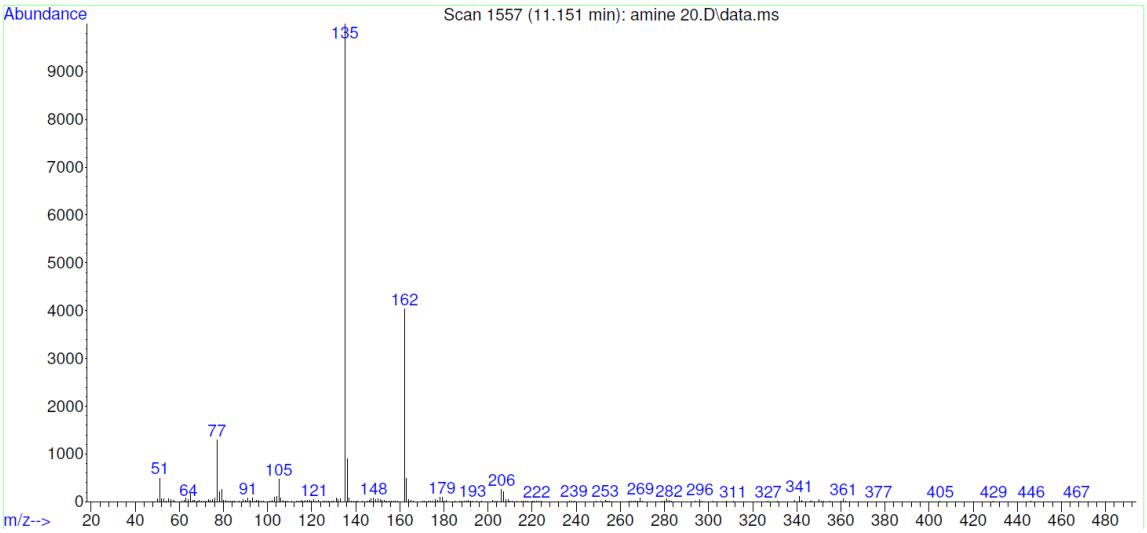


Figure H 11: Mass spectrum for impurity 11

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