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Synthesis and impurity profiling of MDMA prepared from commonly available starting materials

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ABSTRACT

This work examines the synthesis of 3,4-methylenedioxy-N-methylamphetamine (MDMA) from common starting materials that may be utilised by clandestine laboratory operators. Piperonal was prepared from two common starting materials, piperine (from pepper) and vanillin (a common flavouring). Piperine was converted to piperonal by ozonolysis and oxidative cleavage with potassium permanganate and tetrahydrofuran. Vanillin was converted to piperonal by demethylation with pyridine and aluminium chloride followed by methylenation with dichloromethane. The resulting piperonal samples were converted *via* a commonly encountered route to MDMA. The impurities that indicate a particular route were identified and the feasibility of each method was also assessed.

1. Introduction

"Ecstasy" or specifically 3,4-methylenedioxy-N-methylamphetamine (MDMA) is currently one of the most commonly used illicit drugs worldwide [1]. MDMA is an amphetamine type stimulant with mild psychedelic properties. In response to the widespread illegalisation of MDMA, a black market has developed that is supplied by clandestine laboratories. The processes employed in the clandestine manufacture of illicit drugs can give rise to characteristic organic impurities. Knowledge of these impurities may provide useful intelligence about purity, the nature of adulterants and importantly for this work, the synthetic processes and materials used to prepare the drug. Such impurities are commonly identified using mass spectrometry coupled with gas chromatography, although further structure elucidation of the individual impurities can be achieved using nuclear magnetic resonance spectroscopy and infrared spectroscopy.

Most studies involving the impurity profiling of MDMA have focussed on the final synthetic steps [2–8] with little interest in the source of precursors although there are some reports describing precursor analyses [9,10]. Efforts by law enforcement organisations to combat the increase in illicit drug preparation have led to the restricted supply of common precursors such as piperonal (**1**, Scheme 1) and safrole. As these precursors become more difficult to obtain by the clandestine manufacturer, new precursors are likely to emerge. Therefore, an examination of impurities that may arise when new precursors to MDMA are used may prove valuable from a forensic perspective.

The work presented here examines two precursors to MDMA, piperine (**2**, Scheme 1) a component of pepper, and vanillin (**3**, Scheme 1) commonly used in the perfume and flavouring industries. Although literature that aims to inform the clandestine manufacturer is currently available [11], the current study is the first to examine these materials from a rigorous chemical and forensic perspective for the production of MDMA.

Global pepper production in 2010 was 338,000 tonnes, of which Vietnam produced approximately one third. Significant quantities of pepper were also produced in India, Brazil, Indonesia, Malaysia and China [12]. Recent world production of vanillin is of the order of 15,000 tonnes; the majority of which is synthetic [13]. Given the significant quantities of these materials produced globally, there is ample opportunity for their diversion into illicit use.

Piperonal, **1**, was prepared from piperine and vanillin *via* the routes shown in Scheme 1 and the resulting products were converted to MDMA *via* conventional procedures [9,14].

2. Materials and methods

2.1. General

NMR spectroscopy was performed using a Bruker Spectrospin 300 MHz spectrometer and data were processed with Bruker Topspin software. Samples were analysed at room temperature using acetone-d_6 as the solvent. The machine

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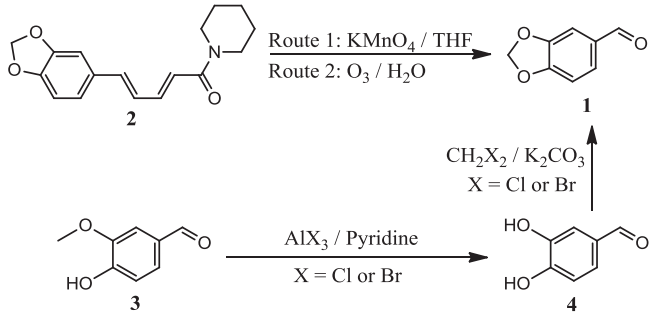


Scheme 1. Conversion of piperine and vanillin to piperonal.

was operated at 300.13 MHz for ^{1}H NMR with 64 scans acquired. Typical acquisition parameters were; spectral width: 8012 Hz, acquisition time: 5.3084 s, relaxation delay: 1.0 s. Chemical shifts (δ) are reported in ppm and the spectra were calibrated using residual protic solvent (2.05 ppm). GC–MS analysis was performed on an Agilent 6890 series gas chromatograph coupled with an Agilent 5973 network mass selective detector and the resulting data processed with MSD Chem Station software. Analytes were separated on a Zebron ZB 5 ms column, 30 m long, with an internal diameter of 0.25 μm. Helium was used as the carrier gas at 1.0 mL/min. The injection volume was 2.0 μL made splitless by the autosampler. The following temperature programme was used; 50 °C maintained for 1 min, then ramped to 150 °C at 10 °C/min, held for 4 min, ramped at 14 °C/min to 290 °C and held for 4 min. Mass spectrometry was performed in positive electron ionisation mode and a full mass spectrum from 29 to 350 amu was obtained. The purity of products was estimated by comparison of the areas (integration) of signals in the ^{1}H NMR spectra.

2.2. Chemicals

Glacial acetic acid, hydrochloric acid (38%), potassium carbonate (anhydrous), sodium chloride, sodium hydroxide and sodium sulphate (anhydrous) were purchased from AJAX Finechem. Ammonium acetate, mercuric chloride, potassium permanganate, petroleum spirits (b.p. 40–60 °C) and sodium hydrogen carbonate were purchased from AJAX Chemicals. Nitromethane, tetrahydrofuran were purchased from BDH Chemicals. Acetone and methanol were purchased from Chem Supply. Nitroethane was purchased from Fluka. Dichloromethane, diethyl ether and toluene were purchased from Lab Scan. Piperonal was purchased from Lancaster. Iron powder was purchased from M&B Chemicals. Aluminium chloride, nicotinic acid, N-methyl-pyrrolidinone, pyridine and vanillin were purchased from Sigma–Aldrich. Calcium hypochlorite and ground pepper were purchased from a local retail department store. Acetone-d_6 was purchased from Cambridge Isotopes. The following reagents were also prepared by the methods shown below:

Aluminium chloride. Concentrated (37%) hydrochloric acid (20 mL, 658 mmol) was added dropwise to hydrated calcium hypochlorite (22.0 g, 102 mmol) generating a steady stream of chlorine gas. The chlorine gas was passed through a glass column filled with aluminium foil (1.00 g, 37.1 mmol) and then into a water trap. Once the apparatus had been filled with chlorine gas the aluminium foil was heated with a bunsen burner to facilitate the reaction. Upon sufficient heating, the aluminium foil burnt with a bright white light signifying the reaction had commenced. At this point the bunsen burner was removed and the reaction self propagated along the column with occasional flickers of red-orange embers. When the vigorous reaction had subsided, a black residue remained in the column and a yellow powder ($AlCl_3$) was deposited in the receiving flask. Yield: 4.05 g (82%).

Pyridine. Nicotinic acid (5.00 g, 40.7 mmol) was heated with a bunsen burner using a distillation apparatus connected to a water trap to collect the flammable pyridine. The nicotinic acid initially melted forming an orange-brown oil that quickly began to bubble and turn black. A yellow liquid condensed and was collected in the receiving flask. The sample was heated until no further liquid condensed. The yellow oil was identified by ^{1}H NMR and GC–MS as pyridine with traces of nicotinic acid and bipyridines. Yield: 1.02 g (32%). ^{1}H NMR: see Fig. S16.

2.3. Extraction of piperine from ground pepper

100 g of ground pepper was suspended in 500 mL of solvent and the resulting mixture stirred at reflux for 2 h. After 2 h the insoluble material was separated by filtration. The dark yellow filtrate containing piperine was concentrated *in vacuo*. The concentrate was dissolved in 100 mL of diethyl ether and the solution concentrated *in vacuo*. A further 100 mL of diethyl ether was added to the concentrate and the insoluble material filtered off. The filtrate was left to cool overnight to yield long, thin, straw-like crystals of piperine. The crystals were collected by filtration and washed with petroleum spirits. Yield: 3.0–3.5 g (see Section 3). ^{1}H NMR: see Fig. S12. GC–MS: see Fig. S1 and S2.

2.4. Piperonal from pepper

2.4.1. Oxidative cleavage of piperine by ozonolysis

A stream of ozone gas, generated by a HAILEA HLO-100 Ozone Steriliser (~100 mg of ozone per hour), was passed through a solution of piperine (1.00 g, 3.51 mmol) in a 5% solution of water in acetone. After 8 h, the ozone generator was switched off and the solution extracted with two 10 mL portions of diethyl ether. The combined ether extracts were dried over anhydrous sodium sulphate and the solvent evaporated *in vacuo* yielding bright yellow oil. Yield: 508 mg (97%). ^{1}H NMR: see Fig. S13. GC–MS: see Fig. 2.

2.4.2. Oxidative cleavage of piperine with aqueous $KMnO_4$ in THF

An aqueous solution of $KMnO_4$ (2.00 g, 12.6 mmol in 40 mL of water) was added dropwise over a period of 4 h to a solution of piperine (1.00 g, 3.51 mmol in 40 mL of THF) at 60 °C. After the solution had been added, the mixture was stirred for 4 h before the MnO_2 precipitate that had formed was filtered off leaving a pale yellow solution. The sample was extracted with diethyl ether and the combined extracts were dried over anhydrous sodium sulphate. The ether was evaporated *in vacuo* to yield a dark yellow-orange oil that solidified on cooling. Yield: 340 mg (65%). ^{1}H NMR: see Fig. S14. GC–MS: see Fig. 2.

2.5. Piperonal from vanillin

2.5.1. 3,4-Dihydroxybenzaldehyde from vanillin

A solution of vanillin (1.00 g, 6.58 mmol) in 100 mL of toluene was added to aluminium chloride (1.15 g, 8.65 mmol) in a two-neck 250 mL round bottom flask. Pyridine (2.50 mL, 31.1 mmol) was added dropwise and the resulting mixture was stirred at reflux for 6 h. Next, 100 mL of dilute hydrochloric acid (15–20%) was added. The organic layer was separated from the aqueous layer, which was then extracted with three 20 mL portions of diethyl ether. The combined ether extracts were dried over anhydrous sodium sulphate and the solvent evaporated *in vacuo* to yield a pale brown solid. Yield: 798 mg (88%). ^{1}H NMR: see Fig. S15.

2.5.2. Piperonal from 3,4-dihydroxybenzaldehyde

To a suspension of K_2CO_3 in 10 mL of N-methyl-pyrrolidinone, a solution of 3,4-dihydroxybenzaldehyde (500 mg, 3.62 mmol) and CH_2Cl_2 (5 mL, 78.3 mmol) in 5 mL of N-methyl-pyrrolidinone was added. The resulting brown mixture was stirred at 120 °C for 3 h. The mixture was allowed to cool and water was added. The sample was extracted with two 20 mL portions of toluene and the combined toluene layers were washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated *in vacuo* to yield a brown oil. Yield: 452 mg (83%). ^{1}H NMR: see Fig. S17.

2.6. MDMA from piperonal

The following procedures were used to prepare MDMA using piperonal prepared by the methods described above as well as from pure piperonal [9,14].

2.6.1. 3,4-Methylenedioxyphenyl-2-nitropropene (MDP2NP) from piperonal

Piperonal (500 mg, 3.33 mmol) was combined with nitroethane (1.0 mL, 1.41 mmol) and ammonium acetate (100 mg, 1.30 mmol) and dissolved in 1.0 mL of glacial acetic acid. The resulting solution was stirred at reflux for 6 h to become dark orange-brown in colour. Next, water was added and the sample extracted with two 10 mL portions of dichloromethane. The combined dichloromethane layers were washed first with 20 mL of a concentrated sodium hydrogen carbonate solution, followed by 20 mL of water, then dried over anhydrous sodium sulphate. The solvent was evaporated *in vacuo* to yield a brown solid. Yield: 584 mg (85%). ^{1}H NMR: see Fig. S18.

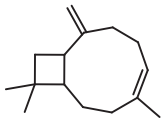
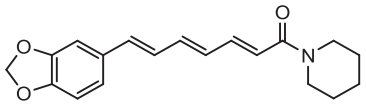
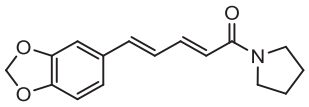
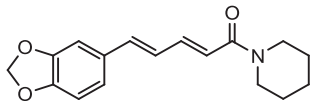
2.6.2. 3,4-Methylenedioxyphenyl-2-propanone (MDP2P) from MDP2NP

To a well stirred suspension of iron pin dust (1.00 g, 17.9 mmol) in 5 mL of glacial acetic acid, a solution of MDP2NP (300 mg, 1.45 mmol) in 10 mL of glacial acetic acid was added. The resulting mixture was stirred at reflux for 2 h. Next, water was added and the mixture filtered to remove any unreacted iron dust. The filtrate was extracted with two 10 mL portions of dichloromethane, and the combined extracts were washed first with 20 mL of concentrated sodium hydrogen carbonate solution, followed by 10 mL of water. The dichloromethane was evaporated, *in vacuo*, yielding a pale brown oil. Yield: 163 mg (63%). ^{1}H NMR: see Fig. S19. GC–MS: see Figs. S6–8.

2.6.3. MDMA from MDP2P

An aluminium amalgam was prepared by mixing 1 cm × 1 cm squares of aluminium foil (140 mg, 5.19 mmol) with a solution of mercuric chloride (40 mg, 147 μmol) in 5 mL of methanol. The resulting mixture was heated to reflux with the aluminium foil turning a dull grey and the appearance of small bubbles of hydrogen on the surface. A solution of nitromethane (100 μL, 1.86 mmol) and MDP2P (100 mg, 562 μmol) in 2 mL of methanol was added and the entire mixture was stirred at reflux for 4 h. Next, a 35% aqueous solution of sodium hydroxide was added dissolving most of the amalgam. The sample was filtered to remove

Table 1
Chemical components of the crystals from pepper.

Compound number	Structure	Name
14		Caryophyllene
15		Piperettine
16		Piperiline
2		Piperine

elemental mercury and any other insoluble material and extracted with two 10 mL portions of toluene. The toluene was evaporated *in vacuo* yielding a brown oil. Yield: 68 mg (63%). ^{1}H NMR: see Fig. S20. GC–MS: see Figs. S9–11.

3. Results and discussion

In each of the syntheses presented here, the procedures were chosen such that they might reflect the capabilities of a moderately equipped clandestine laboratory operated by personnel with basic chemistry knowledge. Rigorous purification of products by sophisticated methods was not undertaken although the techniques of liquid–liquid extraction and crystallisation were included. Importantly, all of the required chemicals were chosen as 'innocuous' or commonplace materials and could be readily sourced by us from commercial or retail suppliers.

3.1. Extraction of piperine from pepper

Commercially ground pepper was used in this study although the unground fruit of the pepper plant (*Piper nigrum*), known as the peppercorn, could also be used. Ground pepper, as the name suggests, is prepared by grinding the peppercorns into a powder. When the peppercorns are ground with the skin still on, ground black pepper is obtained. Alternatively, if the skin is removed from the seed prior to grinding, ground white pepper is obtained.

The gas chromatograms obtained for piperine crystallised from black and white pepper are collected in the Supplementary Information. The impurities include piperiline **16**, piperettine **15**, and in black pepper extract only, caryophyllene **14** (which is much more abundant in the black pepper extract than in the white pepper). The structures of these impurities along with that of piperine **2** are shown in Table 1. Piperettine and piperiline are present in piperine from white pepper in much smaller concentrations for a similar reason.

Chloroform, dichloromethane and methylated spirits were tested to extract piperine from pepper. Chloroform and dichloromethane each yielded ~3.5 g of piperine from 100 g of ground white pepper while methylated spirits yielded 3.0 g of piperine from 100 g of ground white pepper. More piperine was extracted from white pepper than from the same quantity of black pepper.

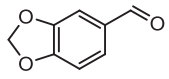
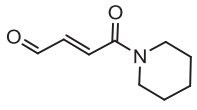
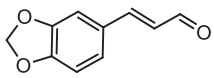
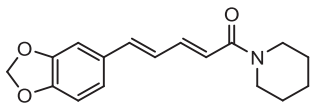
3.2. Preparation of piperonal

The gas chromatograms obtained following synthesis of piperonal from piperine and vanillin (Scheme 1) are presented in Fig. 1. Structures corresponding to the peaks in each chromatogram are presented in Tables 2–4.

3.2.1. Oxidative cleavage of piperine by ozonolysis

Apart from piperonal, only three compounds were consistently detected in samples of piperonal prepared by the ozonolysis of

Table 2
Compounds detected in samples obtained from the ozonolysis of piperine.

Compound number	Structure	Name
1		Piperonal
5		(2E)-4-Oxo-4-piperidin-1-ylbut-2-enal
6		3,4-Methylenedioxycinnamaldehyde
2		Piperine

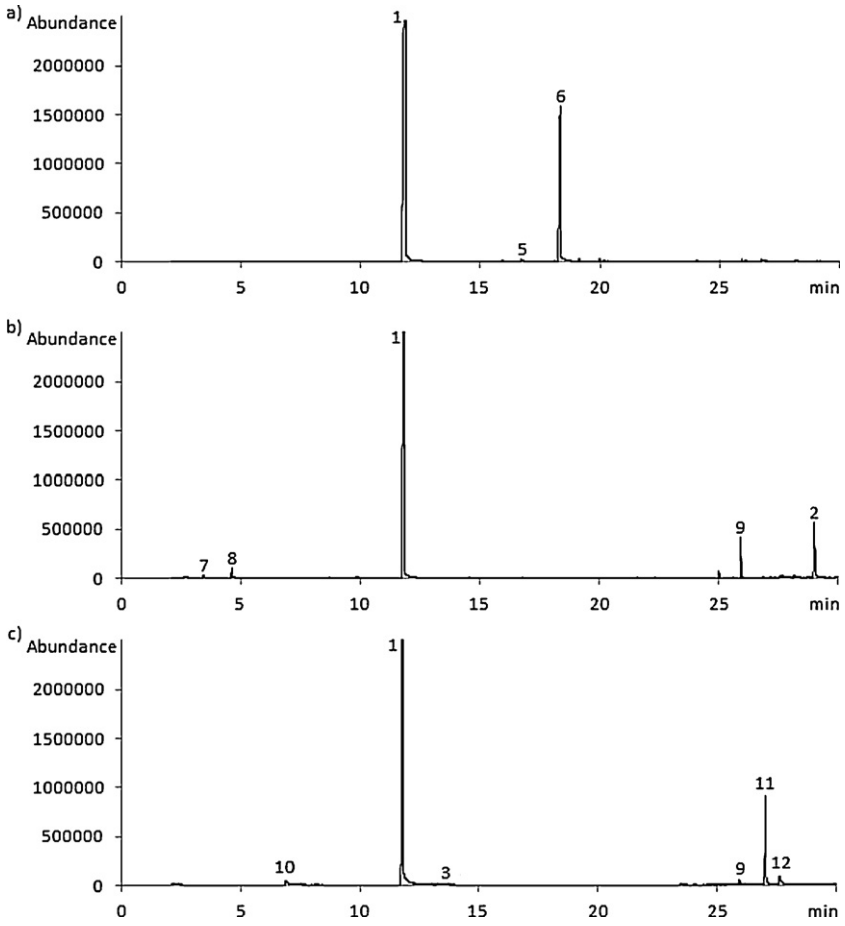


Fig. 1. Gas chromatogram of piperonal from (a) ozonolysis of piperine, (b) oxidative cleavage of piperine with $KMnO_4$/THF and (c) vanillin: see Tables 2–4 for structures.

piperine, two of which could be considered route specific. These were the two possible α,β unsaturated aldehyde products formed when only one alkene bond in piperine is cleaved. Compound **5** is formed alongside piperonal when the double bond closest to the aromatic system is cleaved, while compound **6** is formed when the double bond closest to the piperidine ring is cleaved. The other aldehyde formed in this second process, α-oxo-1-piperidineacetaldehyde, was not detected, possibly because of the enhanced water solubility or hydrolysis to low boiling point products. The yield of **5** is significantly lower than that of piperonal because further cleavage of the remaining alkene group can occur. The structures of **1**, **2**, **5** and **6** are shown in Table 2.

3.2.2. Oxidative cleavage of piperine with $KMnO_4$/THF

Two route specific impurities were consistently identified in samples of piperonal prepared by the oxidative cleavage of piperine with $KMnO_4$. These result from the oxidation of THF (Fig. 2), which is present as a solvent and as an inhibitor of over oxidation of piperonal.

Piperine was also detected in samples of piperonal prepared from piperine indicating incomplete reaction. The presence of

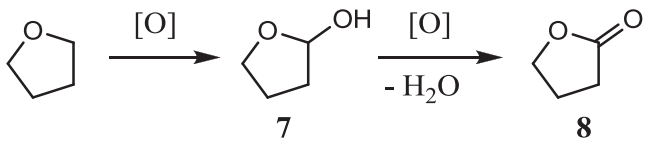


Fig. 2. Production of impurities **7** and **8** from THF.

Table 3
Compounds detected in samples obtained from the oxidative cleavage of piperine with $KMnO_4$ in THF.

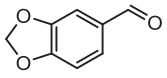
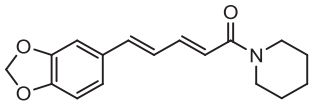
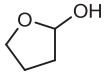
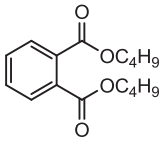
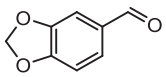
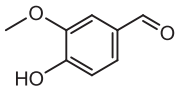
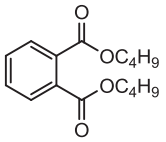
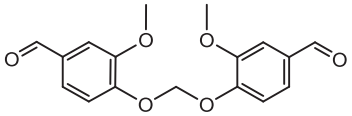
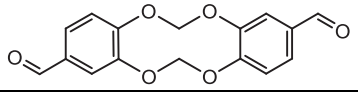
Compound number	Structure	Name
1		Piperonal
2		Piperine
7		2-Tetrahydrofuranol
8		γ-Butyrolactone
9		Dibutylphthalate

Table 4
Compounds detected in samples obtained from the conversion of vanillin to piperonal.

Compound number	Structure	Name
1		Piperonal
3		Vanillin
9		Dibutylphthalate
10		N-Methyl-2-pyrrolidinone
11		Vanillin dimer
12		Piperonal dimer

piperine cannot, therefore, be used to indicate the method used to convert piperine to piperonal, but it does indicate piperine as the starting material Table 3.

3.2.3. Piperonal from vanillin

The conversion of vanillin to piperonal is a two-step process involving demethylation of vanillin followed by methylenation of the resulting 3,4-dihydroxybenzaldehyde (**4**, Scheme 1). Only one major impurity could be detected in samples of 3,4-dihydroxybenzaldehyde, namely the starting material vanillin, reflecting incomplete reaction. The major compounds detected in piperonal prepared from vanillin are shown in Table 4. Compound **11** forms when two molecules of vanillin are joined by a methylenedioxy group. As such it is only detected when the demethylation process is incomplete. In a similar manner, compound **12** forms from two molecules of 3,4-dihydroxybenzaldehyde.

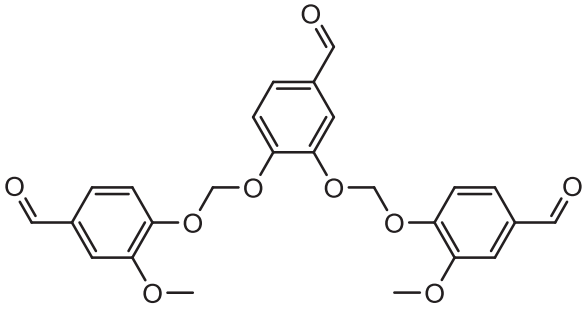


Fig. 4. Proposed structure of the trimer detected in piperonal prepared from vanillin.

The three complex clusters of peaks highlighted in the ^{1}H NMR spectrum in Fig. 3 are believed to arise, in part, from the two major impurities identified by GC–MS, namely the vanillin and piperonal dimers. However, if these were the only compounds giving rise to these peaks, there should be two singlets corresponding to the aldehyde groups at δ 9.5–10, two singlets at δ 5.5–6.0 corresponding to the methylenedioxy groups, and one singlet at δ 3.5–4.0 corresponding to the methoxy groups in the vanillin dimer. The extra peaks in the three clusters of signals suggest that a trimer had also formed. The most likely structure, formed by two vanillin molecules combining with one molecule of 3,4-dihydroxybenzaldehyde, is shown in Fig. 4. It should be noted that these compounds were not isolated and therefore their structural assignments are tentative.

3.2.4. Comparison of routes to piperonal

A comparison of the routes to piperonal examined in this work is summarised in Table 5. The overall yields reported here were determined in terms of moles (*i.e.* moles of product per mole of precursor) as well as mass (*i.e.* grams of product per gram of precursor), with the mass of impurities excluded. Yields for the reactions from piperine are determined from the mass of piperine used rather than the mass of pepper required. However, when the mass of pepper required is considered the overall yields by mass are generally less than 5% since a maximum of 3.5 g of piperine could be obtained from 100 g of pepper.

Overall, none of the methods stood out as being particularly more viable than another as each had its own advantages and disadvantages. While the pepper methods may suit the less experienced clandestine laboratory operator, the greater yields

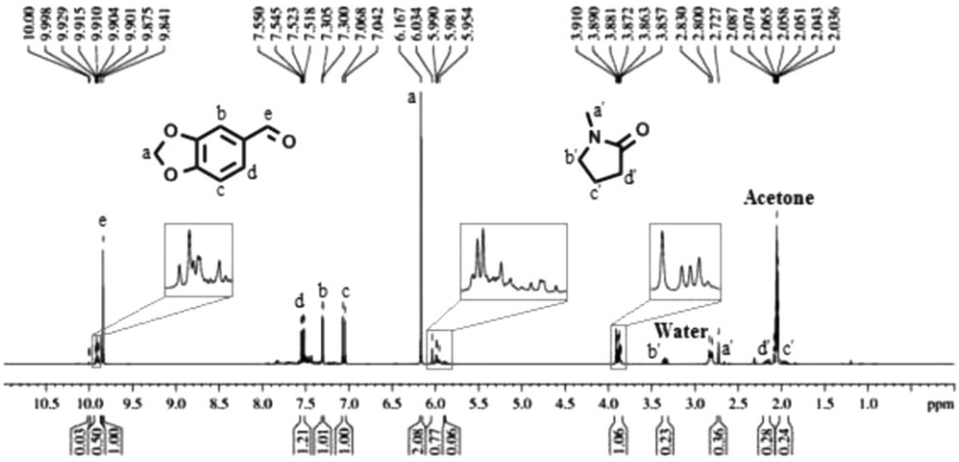
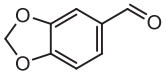
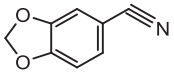
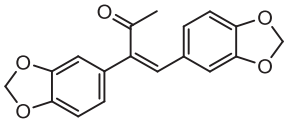
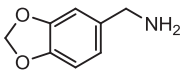
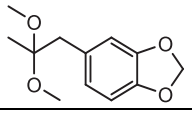


Fig. 3. ^{1}H NMR of piperonal prepared from vanillin in acetone-d_6.

Table 5
Comparison of routes to piperonal.

Precursor	Pepper	Vanillin
Overall yield	*Oxidative cleavage with $KMnO_4$*: 55% by moles and 27% by mass. *Ozonolysis*: 81% by moles and 41% by mass.	50% by moles, and 47% by mass (higher yields can be obtained with longer reaction times).
Ease of reactions	The extraction of piperine from pepper is slightly water sensitive. However, the methods to oxidise piperine are not. Reflux apparatus is not required for any of the methods. Ozone is toxic at high concentrations and is therefore dangerous to handle.	Both reactions are highly water sensitive and both require reflux apparatus. Aluminium chloride is dangerous to handle as it releases HCl gas on contact with atmospheric moisture.
Availability of chemicals	Pepper is commonly used as a spice for cooking. *Extraction*: The solvents used to extract piperine from pepper are common hardware store chemicals. *Oxidative Cleavage with $KMnO_4$*: Potassium permanganate is used as an antiseptic and can be purchased from retail outlets. THF is an industrial solvent for PVC and varnishes. *Ozonolysis*: Ozone is obtained from an ozone generator such as the one used in this study (for aquariums).	Vanillin is a cheap substitute for vanilla extract in perfumes and flavourings. *Demethylation*: The two catalysts involved are not readily available. However they can be prepared from readily available starting materials as demonstrated in this study. The solvents used in this reaction are common hardware store chemicals. *Methylenation step*: Dichloromethane and NMP are often the major components of paint strippers. Sodium bicarbonate is a commonly used in cooking and cleaning.

Table 6
Impurities detected in MDMA, MDP2P and MDP2NP samples regardless of the source of piperonal.

Compound number	Structure	Name	Detected in
1		Piperonal	MDP2NP MDP2P
13		Piperonylonitrile	MDP2NP MDP2P MDMA
14		(3Z)-3,4-Bis(1,3-benzodioxol-5-yl)but-3-en-2-one	MDP2P
15		3,4-Methylenedioxybenzylamine	MDMA
16		MDP2P-dimethylketal	MDMA

obtained from the vanillin route are more beneficial to those with the necessary skills to carry out the more complicated reactions.

3.3. Conversion of piperonal samples to MDMA

The conversion of piperonal to MDMA is generally a three-step process involving an initial Knoevenagel condensation with nitroethane followed by reduction of the resulting MDP2NP to MDP2P. The final step is a reductive amination of MDP2P with nitromethane and aluminium amalgam. The impurities detected in samples of MDMA, MDP2P and MDP2NP that were not dependent on the source of piperonal are shown in Table 6. Impurities dependent on the source of piperonal are discussed in the following sections.

The most significant impurity detected in samples of MDMA prepared by reductive amination in methanol was the ketal impurity **16**. This forms from a side reaction, the mechanism for which is shown in Fig. 5. The required aluminium methoxide is

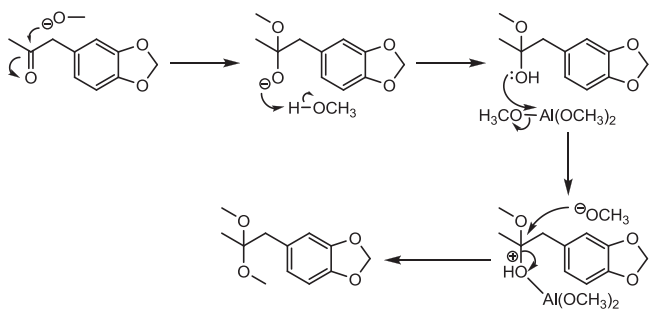


Fig. 5. Mechanism of formation of the ketal impurity.

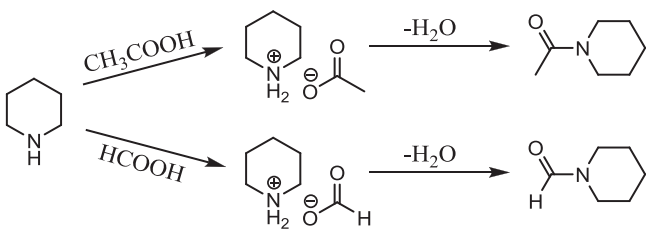


Fig. 6. Formation of N-acetylpiperidine and N-formylpiperidine.

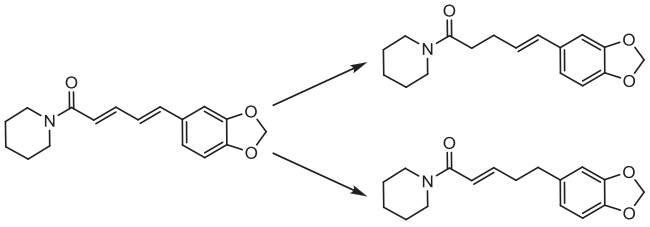


Fig. 7. Reduction of piperine by aluminium amalgam.

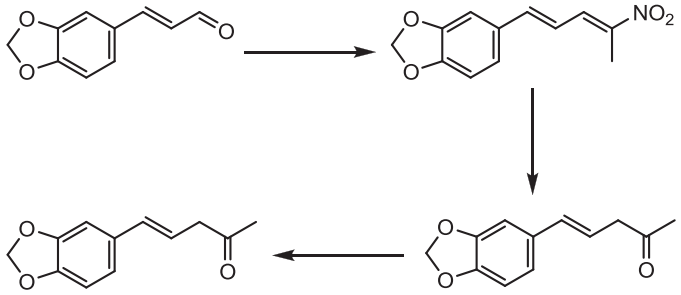


Fig. 8. 3,4-Methylenedioxycinnamaldehyde derived impurities.

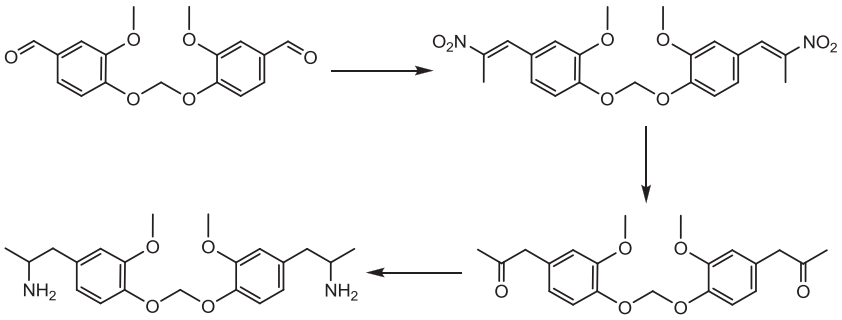


Fig. 9. Vanillin dimer derived impurities.

formed as a byproduct of the production of hydrogen gas according to the following equation:

$$2Al + 6CH_3OH \rightarrow 2Al(OCH_3)_3 + 3H_2$$

Based on this mechanism it is expected that if methanol is replaced by ethanol as the solvent the ethyl derivative will be generated instead.

3.3.1. MDMA from pepper

When piperine was present as unreacted starting material in piperonal, two impurities were formed in MDP2NP. These were N-acetylpiperidine and N-formylpiperidine and they form by a side reaction with the solvent (acetic acid) and a major impurity in the solvent (formic acid) as shown in Fig. 6. Only N-acetylpiperidine was detected in the MDMA product as it was present in much larger amounts compared to N-formylpiperidine. Piperidine is likely to form from the hydrolysis of piperine.

In addition to the two impurities carried through from MDP2NP, two other compounds derived from piperine were detected in MDMA when piperine was the source of piperonal. These were the products of hydrogenation of one double bond in the piperine molecule as shown in Fig. 7. The product formed by hydrogenation of both the double bonds was not detected.

Because the major impurity in piperonal prepared by ozonolysis of piperine was also an aldehyde, it could theoretically react *via* an analogous route to form the impurities shown in Fig. 8. However, only the impurities analogous to MDP2NP and MDP2P were detected in the corresponding samples. This is likely to be a result of the diminishing concentration of the impurity with each step of the synthesis. We note that if pepper has been used as an adulterant in a particular sample of MDMA, then piperine (but not the impurities shown in Figs. 6 and 7) may be present as an impurity.

3.3.2. From vanillin

Similarly to the major impurity in piperonal prepared by the ozonolysis of piperine, the two major impurities detected in piperonal prepared from vanillin were also aldehydes that could react *via* an analogous route to form new route specific impurities. The impurities derived from the vanillin dimer are shown in Fig. 9.

4. Conclusions

Piperonal was prepared from two readily available sources, namely piperine and vanillin, in reasonable yields. Vanillin was converted to piperonal by a two-step process involving initial demethylation, with an 88% yield and purity of 72%, followed by methylenation, with a 90% yield and purity of 65%. Piperine, extracted from ground white pepper, was converted to piperonal by two different one-step processes. The first involved oxidative cleavage using $KMnO_4$, with a yield of 65% and a purity of 78%. The second involved ozonolysis with a yield of 97% and a purity of 81%.

The feasibility of each of the methods to prepare piperonal was examined by considering the overall yield, availability of precursors, and the difficulty of the associated processes. Overall, neither of the precursors stood out as being more viable than the other. While the routes from pepper may be better suited to the less skilled operator, a more experienced chemist would benefit more from the greater yields obtained from the vanillin route.

Samples of piperonal were converted to MDMA in a three-step process *via* MDP2NP and MDP2P. The first step, involving a condensation reaction of nitroethane with piperonal, was achieved with a yield of 85% and a purity of 85%. The next step, in which the resulting MDP2NP was reduced with iron in glacial acetic acid to form MDP2P, was achieved with a yield of 63% and a purity of 87%. The final step, a reductive amination where methylamine was generated *in situ* from nitromethane, was achieved with a yield of 63% and a purity of 55%. The low purity of the MDMA resulting from this synthesis was attributed to the significant competing reaction (between the solvent and MDP2P).

Samples of piperonal prepared by each of the three routes could be readily differentiated by ^{1}H NMR and GC–MS. Samples containing butyrolactone, from the oxidation of THF, were assigned to the $KMnO_4$/THF oxidative cleavage of piperine. These samples also contained piperine although this was not considered route specific. Samples prepared by the ozonolysis of piperine were contaminated with 3,4-methylenedioxycinnamaldehyde from the partial ozonolysis of piperine. Finally, samples containing the vanillin and piperonal dimers were assigned to the demethylation and subsequent methylenation of vanillin.

Samples of MDMA prepared from piperonal could not be readily differentiated by ^{1}H NMR because of the low concentration of route specific impurities. However, GC–MS analysis allowed the precursor to piperonal to be identified, although the different routes from these precursors to piperonal could not be readily identified. Samples prepared from vanillin contained the MDMA dimers resulting from the vanillin and piperonal dimers. Samples prepared from piperine contained N-acetyl piperidine and, when unreacted piperine was present, the two dihydropiperine isomers.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.forsciint.2012.10.006.

References

[1] UNODC, World Drug Report, United Nations Publication (2011).
[2] M. Świst, J. Wilamowski, A. Parczewski, Determination of synthesis method of ecstasy based on the basic impurities, Forensic Sci. Int. 152 (2005) 175–184.
[3] M. Świst, J. Wilamowski, A. Parczewski, Basic and neutral route specific impurities in MDMA prepared by different synthesis methods: comparison of impurity profiles, Forensic Sci. Int. 155 (2005) 100–111.
[4] R.J. Renton, J.S. Cowie, M.C.H. Oon, A study of the precursors, intermediates and reaction by-products in the synthesis of 3,4-methylenedioxymethylamphetamine and its application to forensic drug analysis, Forensic Sci. Int. 60 (1993) 189–202.
[5] A. Verweij, Clandestine manufacture of 3,4-methylenedioxymethylamphetamine (MDMA) by low pressure reductive amination. A mass spectrometric study of some reaction mixtures, Forensic Sci. Int. 45 (1990) 91–96.
[6] M. Bohn, G. Bohn, G. Blaschke, Synthesis markers in illegally manufactured 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine, Int. J. Legal Med. 106 (1993) 19–23.
[7] Q. Milliet, C. Weyermann, P. Esseiva, The profiling of MDMA tablets: a study of the combination of physical characteristics and organic impurities as sources of information, Forensic Sci. Int. 187 (2009) 58–65.
[8] C. Weyermann, R. Marquis, C. Delaporte, P. Esseiva, E. Lock, L. Aalberg, J.S. Bozenko Jr., S. Dieckmann, L. Dujourdy, F. Zrcek, Drug intelligence based on MDMA tablets data: I organic impurities profiling, Forensic Sci. Int. 177 (2008) 11–16.
[9] M. Świst, J. Wilamowski, D. Zuba, J. Kochana, A. Parczewski, Determination of synthesis route of 1-(3,4-methylenedioxyphenyl)-2-propanone (MDP-2-P) based on impurity profiles of MDMA, Forensic Sci. Int. 149 (2005) 181–192.
[10] P. Gimeno, F. Besacier, M. Bottex, L. Dujourdy, H. Chaudron-Thozet, A study of impurities in intermediates and 3,4-methylenedioxymethamphetamine (MDMA) samples produced via reductive amination routes, Forensic Sci. Int. 155 (2005) 141–157.
[11] Rhodium: Drug Chemistry Archive, 2004. Available from: http://www.erowid.org/archive/rhodium/chemistry/index.html (cited 06.03.12).
[12] International Pepper Community, Pepper Statistics 2001–2010, Online Report available from www.ipcnet.org.
[13] R.L. Myers, The 100 Most Important Chemical Compounds: A Reference Guide, Greenwood Press, Westport, CT, 2007, , ISBN: 978-0313337581.
[14] I. Billault, F. Courant, L. Pasquereau, S. Derrien, R.J. Robins, N. Naulet, Correlation between the synthetic origin of methamphetamine samples and their ^{15}N and ^{13}C stable isotope ratios, Anal. Chim. Acta 593 (2007) 20–29.