A review of impurity profiling and synthetic route of manufacture of methylenedioxymethylamphetamine, 3,4-methylenedioxymethylamphetamine, amphetamine, dimethylamphetamine and p-methoxyamphetamine

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A B S T R A C T
Amphetamine-type substances (ATS), like other synthetically derived compounds, can be produced by a multitude of synthetic pathways using a variety of precursors and reagents, resulting in a large number of possible contaminants (by-products, intermediates and impurities). This review article describes the common contaminants found in preparations of methamphetamine (MA), 3,4-methylenedioxymethylamphetamine (MDMA), amphetamine (AP), N,N-dimethylamphetamine (DMA) and p-methoxyamphetamine (PMA) synthesised via common synthetic pathways including reductive amination, Leuckart method, Nagai method, Emde method, Birch reduction, "Moscow" method, Wacker process, "Nitrostyrene" method and the Percacid oxidation method.

Contaminants can facilitate identification of the synthetic route, origin of precursors and may suggest information as to the location of manufacture of these illicit drugs. Contaminant profiling can provide vital intelligence for investigations in which linking seizures or identifying the synthetic pathway is essential. This review article presents an accessible resource; a compilation of contaminants resulting from a variety of manufacturing methods used to synthesise the most common ATS. It is important for research in this field to continue as valuable information can be extracted from illicit drug samples, increasing discrimination amongst ATS, and in turn, leading to an increase in evidential value and forensic drug intelligence from forensic drug samples.

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1. Introduction

Recreational use of non-medically accepted drugs is a phenomenon that has been apparent for many years. The amphetamine-type substances (ATS) such as amphetamine (AP), methamphetamine (MA), 3,4-methylenedioxymethamphetamine (MDMA), and 3,4-methylenedioxyamphetamine (MDMA) are particularly popular drugs of abuse [1]. ATS are sometimes collectively referred to as phenethylamines due to a common structural moiety.

According to the United Nations Office on Drugs and Crime (UNODC), ATS are firmly established on the illicit drug market, with global use continuing to exceed that of cocaine and heroin combined [2]. In Australia, ATS are the second most commonly used illicit drugs, only after cannabis [1]. In East and South-East Asia, as well as in the Middle East, consumption of ATS, particularly MA, is increasing [1].

Profiling of ATS, based upon the presence of traces of by-products, intermediates and impurities can provide useful information in criminal investigations and, specifically, on drug trafficking routes, sources of supply, and relationships between seizures [3]. In this article the word by-product will be used to describe compounds that arise from reactions that compete with the formation of the desired product (i.e. products of a side reaction). This includes reactions where the desired product, once it has been formed, undergoes reaction with starting materials. By-products will therefore arise in a synthetic method no matter how pure the reagents or precursor are. Of particular importance are the so-called route specific by-products that suggest the particular method used in the synthesis of the drug. It should be pointed out, however, that the research leading to the identification of a number of route-specific by-products has been relatively limited in scope. For example, the finding was made that certain naphthalenes are route-specific by-products in the Nagai reaction for the production of MA simply by conducting the reaction under controlled conditions and identifying that the naphthalenes were present after the reaction was completed, rather than by searching for the presence of these naphthalenes in a wide range of different MA syntheses. As is indicated below, naphthalenes can be produced when a key precursor, phenyl-2-propanone (P-2-P), is heated in the presence of acid, therefore rather than being route-specific certain by-products should perhaps be considered condition-specific. Several articles are cited below where the concept of route-specific by-products is being challenged.

In some syntheses the product is produced as a result of two consecutive steps, where the precursor is converted into a compound that is in turn converted into the product; in this article the word intermediate will be used to describe the product of the first step.

Many precursors and reagents contain additional compounds, that is, they are not absolutely pure. The word impurities will be used to describe these additional compounds, or products arising from reactions of these compounds, that appear in the desired product of the synthesis. Clearly if starting materials are rigorously purified then the final product will not contain impurities but it can contain by-products. The word contaminant will be used as a collective term for by-products, intermediates and impurities (i.e. anything detected in final product other than the desired compound).

ATS may be produced by numerous synthetic pathways using a variety of precursors and reagents, resulting in a vast number of possible contaminants. Furthermore, Sanger et al. [4], established that variation in profiles (i.e. the relative abundance of the major by-products, intermediates and impurities) are observed, even when the same synthetic reaction is strictly followed by different chemists. Profile variations are also obtained by the same chemist following the same procedure to produce more than one batch. For each stage of a reaction, varying the reaction conditions leads to a change in the profile. Therefore, when a number of illicit drug samples are found with similar profiles there is support for the hypothesis that they came from the same batch, with the strength of support increasing as profiles become more complex [4]. While inter-batch variation can be used to distinguish two samples, it cannot be used to determine whether the same chemist or different chemists were involved in the manufacture.

The detection of route-specific by-products or intermediates can be used to determine the route of manufacture, that through fusion with other forms of intelligence, might allow linking of batches to the 'cook' that synthesised the drugs. This is beyond the scope of this study.

This review provides an overview of the characteristic by-products, intermediates and impurities resulting from the manufacture of AP, MA, MDMA, N,N-dimethylamphetamine (DMA) and p-methoxyamphetamine (PMA) and their key precursors via some common synthetic routes. Fig. 1 depicts the most common manufacturing routes for the production of MA, including the Leuckart method [5], reductive aminations [5], Nagai method [6], "Moscow" method [7], Birch reduction (also known as "Nazi" method) [8,9], and Emde method [6]. The manufacture of MDMA, AP, DMA, and PMA (Figs. 2–5) follow similar reaction pathways when suitably substituted precursors are used, which can be prepared via synthetic methods such as the Wacker process [10] and peracid oxidation [11].

It is important to note that this article does not present an exhaustive list of compounds found in all ATS preparations nor
does it cover every published synthetic route to ATS, just the more common ones (see Table 1 for a list of the most characteristic compounds and see also Supplementary data: Tables S1–S5 for a comprehensive list of all the by-products, intermediates and impurities mentioned in this article).

### 1. Common synthetic routes for MA manufacture

- **Nagai (H2, HgCl2)**: (Z)-N-methyl-N-(α-methylphenylethyl)-3-phenylpropanamide B4.
- **Emde**: Chlorophedrine/chloroephedrine C1, methylephedrine C2, N-formylephedrine C3, N-acetylemphetamine C6.

### 2. Common synthetic methods in the manufacture of ATS

The Leuckart reaction is very important in the synthesis of ATS because it is a method that is generally applicable to the synthesis of a wide range of amphetamines from starting materials that can

<table>
<thead>
<tr>
<th>Compound</th>
<th>Synthetic route</th>
<th>Characteristic contaminants</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA (refer to Fig. 6)</td>
<td>Reductive amination</td>
<td>1-Phenyl-2-propanol A1, amphetamine A2, 1,3-diphenyl-2-methylaminopropane A3, N-cyanomethyl-N-methyl-1-phenyl-2-propylamine A4, N,N,N-trimethylephedrine B1, N-(1-phenylpropan-2-yl)prop-2-enamide (cis-cinnamoyl derivative of MA) B2, N-methyl-N-(α-methylphenyl)amino-1-phenyl-2-propanone B3, (Z)-N-methyl-N-(α-methylphenylethyl)-3-phenylpropanamide B4</td>
</tr>
<tr>
<td>MDMA (refer to Fig. 7)</td>
<td>Reductive amination</td>
<td>3,4-Methylenedioxy-N-methylbenzylamine A5, 4,5-methylenedioxy-3-(3,4-methylenedioxyphenyl)-1,3-dioxolan-2-one A6, N-methyl-2-methoxy-1-methyl-2-(3,4-methylenedioxyphenyl)-ethanamine A7, N-cyclohexyloxycetanilide A8, 1,2,2,4-bis-(1,3-benzodioxol-5-ylmethyl)pyridine A9, N-cyanomethyl-N-methyl-1-(3,4-methylenedioxyphenyl)-2-propylamine A10, 1-(3,4-methylenedioxy)phenyl-2-propyl)methamphetamine (MDMA dimer) A11</td>
</tr>
<tr>
<td>Leuckart</td>
<td>α-Benzyl-N,N-dimethylethylamine B1, α,α′-dimethylidiphenylethylamine B2, N-acetylamphetamine B3, 1-(4-Trimethylammonium)benzyl-3-(3,4-ethylenedioxyphenyl)-propanoate B4</td>
<td></td>
</tr>
<tr>
<td>Leuckart</td>
<td>p-Bromotoluene F4, N-ethylamphetamine F5, N-ethylmethamphetamine F6, N-formylamphetamine F7, N-formyl MDMA F8, 5-[1-(1,3-benzodioxol-5-ylmethyl)pyridine F9, 3,4-bis-(1,3-benzodioxol-5-ylmethyl)pyridine F10, 1-(3,4-Methylenedioxy)phenyl-2-propyl)methamphetamine (MDMA dimer) A12</td>
<td></td>
</tr>
<tr>
<td>Leuckart</td>
<td>N-formylmethamphetamine F9, 4-benzylpyrimidine F10, 4-benzyl-5-phénylpyrimidine F11, 2,4-dimethyl-3,5-diphenylpyridine F12, 2,6-dimethyl-3,5-diphenylpyridine F13</td>
<td></td>
</tr>
<tr>
<td>Leuckart</td>
<td>α-Benzyl-N,N-dimethylethylamine B1, α,α′-dimethylidiphenylethylamine B2, N-acetylamphetamine B3, 1-(4-Trimethylammonium)benzyl-3-(3,4-ethylenedioxyphenyl)-propanoate B4</td>
<td></td>
</tr>
<tr>
<td>AP (refer to Fig. 8)</td>
<td>Reductive amination</td>
<td>Chlorophedrine/chloroephedrine C7, 1-(3,4-methylenedioxy)phenyl-2-propyl)methamphetamine (MDMA dimer) A12</td>
</tr>
<tr>
<td>AP (refer to Fig. 8)</td>
<td>Oxidation</td>
<td>Chlorophedrine/chloroephedrine C7, 1-(4-Trimethylammonium)benzyl-3-(3,4-ethylenedioxyphenyl)-propanoate B4</td>
</tr>
<tr>
<td>DMS (refer to Fig. 9)</td>
<td>Nitroso-N-oxide</td>
<td>2-Nitroprop-1-enylbenzene I1, benzoylethyl ketoxime I2, N-(β-phenylisopropyl)benzaldehyde I3, 1-Propenylbenzene B5, 2-propenylbenzene B6</td>
</tr>
<tr>
<td>DMS (refer to Fig. 9)</td>
<td>Oxidation</td>
<td>Chlorophedrine/chloroephedrine C7, 1-(3,4-methylenedioxy)phenyl-2-propyl)methamphetamine (MDMA dimer) A12</td>
</tr>
<tr>
<td>PMA (refer to Fig. 10)</td>
<td>Reductive amination</td>
<td>4-(4-Methoxyphenyl)pyrimidine F16,4-(3,4-methylenedioxyphenyl)pyrimidine F17, 2,4-dimethyl-3,5-di-(4-methoxyphenyl)pyridine (F18), 2,6-dimethyl-3,4-di-(4-methoxyphenyl)pyridine (F19)</td>
</tr>
<tr>
<td>PMA (refer to Fig. 10)</td>
<td>Oxidation</td>
<td>4-Methoxyphenol H7</td>
</tr>
</tbody>
</table>
be readily sourced by legal or illegal means (i.e. P-2-P and its analogues). The reaction was first described by Leuckart in 1885 [12], who used ammonium formate or formamide, and was then elaborated upon in 1893 by Wallach [13] who used ammonium formate in the presence of excess formic acid. The former reaction is called the Leuckart reaction and the latter the Leuckart–Wallach reaction; it is common in the literature for the Leuckart–Wallach reaction and another variant where formamide is used to be referred to simply as the Leuckart reaction and that convention will be followed here. Landmark publications in 1944 [14] and 1949 [15] provided discussions as to the mechanism of the reductive alkylation, although debate as to the exact detail of the mechanism was still taking place in 1963 [16] and 1999 [17]. In the context of ATS synthesis the Leuckart reaction is defined as a reductive alkylation (with P-2-P or one of its analogues being the alkylating agent) of an amine (ammonia or methylamine) with formic acid.

Fig. 2. Common synthetic routes of MDMA manufacture.

Fig. 3. Common synthetic routes of AP manufacture.
acting as the reducing agent. The reaction product is a formylamphetamine that is hydrolysed in aqueous acid to produce the corresponding amphetamine.

Reductive amination is also a generally applicable reaction that involves the treatment of one of the ketones listed above with an amine (e.g. methylamine or ammonia) to form a hemiaminal species that is then converted to an intermediate imine. Reducing agents such as sodium cyanoborohydride, sodium borohydride or aluminium in the presence of mercury chloride catalyst are used to reduce the imine to the corresponding ATS (Figs. 1–5). Although it is an old reference, the review of synthetic reductions by Allen et al. [18] is still relevant.

Several variations of the reduction of L-ephedrine or D-pseudoephedrine to MA via iodoephedrine or iodopseudoephedrine exist; these include the Nagai method, “Moscow” method, and the “Hypo” method (Fig. 1). The Nagai method employs hydriodic acid and red phosphorus [19,20], whereas the others generate hydriodic acid in situ using iodine and red phosphorus (“Moscow” method [21]) or iodine and either hypophosphorous acid or phosphoric acid (“Hypo” method [22]). These methods are popular due to their ability to produce end products that are enantiomerically pure, i.e. the more potent D-MA.

The dissolving metal reductions, sometimes called the Birch reduction [23], were first described as being used in clandestine laboratories by Ely and McGrath [9]. Since that time the use of this method has become increasingly common for the synthesis of MA. In this method, a metal such as metallic lithium or metallic sodium is reacted with L-ephedrine or D-pseudoephedrine (or, as indicated...
3. Common methods for the synthesis of precursors

3.1. Phenyl-2-propanone (P-2-P)

P-2-P is a key precursor that is usually prepared from either phenylacetic acid or benzaldehyde, although allyl benzene or even benzene can be used. In the former case, phenylacetic acid is treated either with lead acetate at high temperature or a mixture of acetic anhydride and sodium acetate or pyridine at reflux [18,27]. In the case of benzaldehyde, it is treated with nitroethane to produce β-methyl-β-nitrostyrene that is then directly reduced to P-2-P using iron and hydrochloric acid [28] or partially reduced to phenyl-2-propylketimine that is hydrolysed to P-2-P [29].

The reaction between phenylacetic acid and acetic anhydride is complex but is well described by Allen et al. [18]. Although Allen et al. do postulate a mechanism for the lead acetate conversion of phenylacetic acid into P-2-P [18], the exact mechanism is obscure. In any event, the complexity of both of these synthetic procedures ensures that many competing side reactions take place and as a result a multitude of by-products are produced. Allen et al. [18] indicate that route-specific by-products that could be detected in illicit P-2-P or crude reaction mixtures are the E- and Z-isomers of P-2-P enol acetate for the method using acetic anhydride and dibenzyl and diphenylmethylene for the method using lead acetate. A range of non route-specific olefins (E- and Z-1-phenyl-2-benzyl-1-propene and 1-phenyl-2-benzyl-2-propene) [18,30] and other aromatics [18] have also been described in the synthesis of P-2-P from phenylacetic acid but of particular relevance is the production of dibenzyl ketone as a by-product. This ketone is difficult to separate from P-2-P therefore non-commercial P-2-P will most likely contain dibenzyl ketone and it will undergo the same reactions as P-2-P to form 1,3-diphenyl-2-amino propane in the case of AP synthesis or 1,3-diphenyl-2-methylaminopropane (structure A3) in the case of MA synthesis.

3.2. Pseudoephedrine and ephedrine

By far the largest source of pseudoephedrine and ephedrine in the illicit manufacture of MA is commercial material, either diverted in its pure form or extracted from medications such as cold and flu tablets [31]. Ultimately the sources of this commercial material are the Ephedra plant or by the biotransformation of benzaldehyde. Clandestine syntheses of ephedrine/pseudoephedrine are encountered less regularly due to lengthy procedures needed resulting in racemic mixtures of ephedrine/pseudoephedrine subsequently requiring enantiomeric purification prior to conversion to their illicit end-product.

The extraction of pseudoephedrine from medications is straightforward but the process will also extract other active ingredients that can be carried through the subsequent chemistry used to convert pseudoephedrine into MA. In addition, Pigou [32] found that the use of ethanol or methanol in the extraction of pseudoephedrine from medications leads to the formation of N-ethyl- and N-methyl-ephedrine, respectively, when the “Hypo” method is used.

Barker and Antia [24] discuss the illicit extraction of Ephedra plants and indicate that as well as ephedrine and pseudoephedrine the related congeners methylpseudoephedrine, methylpseudoephedrine, norpseudoephedrine and norpseudoephedrine are extracted. These behave analogously to ephedrine and pseudoephedrine in MA-forming reactions to form DMA and AP, respectively (Figs. 4 and 3).

The use of the biotransformation process in clandestine laboratories has only been reported once [33]. Fermentation of glucose with yeast leads to pyruvic acid and then acetaldehyde, which in the presence of benzaldehyde condenses to form 1-hydroxy-1-phenylpropanone (also known as γ-phenylacetylcarbinol or γ-PAC). This hydroxketone is converted into ephedrine and pseudoephedrine upon treatment with methyleamine and sodium borohydride. 1-Phenyl-1,2-propanedione and 2-hydroxy-1-phenyl-1-propanone by-products are formed in the fermentation and these are carried through to 1-phenyl-1,2-diaminopropane (two diastereoisomers) and 1-phenyl-1-amino-2-hydroxypropane (also two diastereoisomers), respectively, upon reductive amination (each by-product was unambiguously identified by independent synthesis). When ephedrine and pseudoephedrine contaminated with these compounds are subjected to the “Hypo” method the expected impurities are detected in the MA product, as described in more detail below.

Armellin et al. [34] detailed the synthesis of ephedrine or pseudoephedrine through the bromination of propiophenone. The resulting 2-bromo-1-phenylpropan-1-one is then reacted with methyleamine to form 2-(methylamino)-1-phenylpropan-1-one that is subsequently reduced to produce a racemic mixture of ephedrine and pseudoephedrine. With an increase in “distance” between the final product and precursor comes less regulation of the precursor. However, lengthy synthetic processes will inevitably result in lower yields and slower production of final product. Further to this, the racemic mixture obtained for ephedrine and pseudoephedrine will require resolution if d-MA is the target. These drawbacks possibly indicate why few instances of the conversion of propiophenone into MA have been reported.

3.3. 3,4-Methylenedioxyphenyl-2-propanone and 4-methoxyphenyl-2-propanone

Percid acid or chrome oxidation of isosafrole or anethole has been used in the synthesis of 3,4-methylenedioxyphenyl-2-propanone (3,4-MDP-2-P) and 4-methoxyphenyl-2-propanone (PMP-2-P) (Figs. 2 and 5). The olefins are converted into intermediate diols, which undergo pinacol-type rearrangement under acidic conditions to produce the ketones [11].
Gimeno et al. [3] reported that 3,4-methylenedioxybenzaldehyde and 1-(3,4-methylenedioxyphenyl)-1-propane (structure H3) were significant by-products in 3,4-MDP-2-P prepared using both oxidative methods together with two reduction products (dihydrosafrole and 3,4-methylenedioxyisohydrin) and two methoxylated compounds, 1-(4-methoxyphenyl)-2-propanone and 1-(3,4-methylenedioxyphenyl)-2-propanone (structure H2). The latter methoxylated compound and 3,4-methylenedioxypropionophenone (structure H3) were not detected in 3,4-MDP-2-P prepared by oxidation/hydrolysis of 3,4-methylenedioxyphenylisopropanone (see below) and therefore appear to be specific to the peracid or chromate oxidation of isosafrole. Gimeno took the crude 3,4-MDP-2-P prepared by the oxidation of isosafrole and subjected it to reductive aminations. As expected the dimethoxyketone (structure H2) yielded a secondary amine but the structure for the product (structure “8methyl”) drawn by Gimeno is not correct, although it is named correctly. The intermediate diol was rarely detected in 3,4-MDP-2-P. In the same article Gimeno et al. also examined the fate of contaminants present in commercial isosafrole and that sourced from sassafras oil. They found 1-methoxy-4-(1-propenyl)benzene, sasaffrole and 1,2-dimethoxy-4-(1-propenyl)benzene to be present in both forms of isosafrole and these were oxidised in a manner analogous to that of isosafrole to produce 1-(4-methoxyphenyl)-2-propanone and 1-(3,4-dimethoxyphenyl)-2-propanone (structure H2) impurities in the final material. Unambiguous assignment of these structures through independent synthesis was not described.

Swist et al. [36] agreed with Gimeno et al. [3] that 3,4-methylenedioxypropionophenone (structure H3) is an important contaminant in the oxidation of isosafrole. However, they did not report the presence of either of the methoxylated ketones described by Gimeno et al. Swist et al. also reported the presence of other significant compounds (unambiguous assignment of these structures through independent synthesis was not described); these were 1-(3,4-methylenedioxyphenyl)-1-methoxypropan-2-one (structure G1), 2,2,4-trimethyl-5-(3,4-methylenedioxyphenyl)-1,3-dioxolane (structure H4), 1-(3,4-methylenedioxyphenyl)-1,2-propane dione (structure H5), 1-(3,4-methylenedioxyphenyl)-1-propanone (structure H3), 1-methoxy-1-(3,4-methylenedioxyphenyl)-2-propanol (structure H6) and 4-methyl-5-(3,4-methylenedioxyphenyl)-1,3-dioxolan-2-one (structure A6) as route-specific by-products. Swist et al. [36] conducted their oxidation using aceton as solvent, which would account for the formation of the dioxolane and the dioxolane that were not detected by Gimeno et al. [3]. Although it was reported that the dioxolane readily converts into 3,4-MDP-2-P and does not tend to carry-through subsequent chemistry the dioxolane does. Swist et al. [36] also analysed their (commercial) isosafrole for contaminants and detected terpineol, thymol, 1,7-dimethyl-7-(4-methyl-3-pentenyl)-tricyclo[2.2.1.02,6]heptane, 2,6-dimethyl-6-(4-methyl-3-pentenyl)-bicyclo[3.1.1]hept-2-ene and 3,4-methylenedioxbenzaldehyde. Under the oxidative conditions that are used to form 3,4-MDP-2-P the unsaturated moieties in 1,7-dimethyl-7-(4-methyl-3-pentenyl)-tricyclo[2.2.1.02,6]heptane was found to react to form 1-(2,3-dimethyltricyclo[2.2.1.02,6]hept-3-yl)-4-methylpentan-3-one.

In a study conducted by Cox et al. [37], the chemical markers for the peracid oxidation of isosafrole have been identified (Fig. 3). It was found that 2,4-dimethyl-3,5-bis(3,4-methylenedioxyphenyl)-tetrahydrofuran (structure H1) is produced as a mixture of three diastereomeric isomers. The most abundant stereoisomer formed contains a 2,3-cis, 3,4-trans, 4,5-trans configuration, while the next most abundant diastereoisomer contains the all cis configuration. Waumans et al. [38] reported upon the peracid oxidation of anisole present in anise oil to yield PMP-2-P. These authors mentioned the detection of the intermediate glycol and its formate ester but do not mention the presence of any by-product compounds analogous to those reported by Cox et al. [37]. Waumans et al. did however report a number of impurities arising from the anise oil starting material, especially 4-methoxyphenol (which confirmed the earlier detection of this compound in illicit PMA tablets by Coubbaro et al. [39]) and its formate ester. The authors postulated that 4-methoxyphenol (Fig. 10, structure H7) arises from the Baeyer-Villiger oxidation of 4-methoxybenzaldehyde, which is present in anise oil as an impurity. This hypothesis is supported in the literature by Godfrey et al. [40], who converted a number of methoxybenzaldehydes into methylenophenols using m-chloroperbenzoic acid. Waumans et al. also report that whilst anise oil contains 4-methoxybenzaldehyde it does not contain 4-methoxyphenol; star anise oil contains both the aldehyde and the phenol. Both types of oils contain a multitude of other natural products like limonene, borneol, camphor, etc. that would be detected in crude PMP-2-P derived from anise oil. It would appear that 4-methoxyphenol is difficult to remove from 4-methoxyphenol-2-propanone because it has been identified as an impurity in illicit PMA tablets [39].

Gimeno et al. [35] studied the production of 3,4-MDP-2-P from the oxime of 3,4-MDP-2-P, which in turn was produced by iron/acetic acid reduction of the condensation product between 3,4-methylenedioxybenzaldehyde and nitroethane (i.e. 3,4-methylenedioxyphenylisopropanone). Even though the oxime is an intermediate in this reaction Gimeno et al. reported that it is rarely detected in the final product. The authors found that the only difference between 3,4-MDP-2-P synthesised from the nitrostyrene and that produced by oxidation of isosafrole is that 3,4-methylenedioxypropionophenone (structure H3) and 1-(3,4-methylenedioxyphenyl)-2-propanone (structure H2) are not by-products of the oxidation/hydrolysis route. Swist et al. [36] also studied the 3,4-methylenedioxyphenylisopropanone route to 3,4-MDP-2-P and used acetic acid and cyclohexylamine to catalyse the condensation. They indicated that 3-methyl-6,7-methylenedioxyisoquinoline-1,4-dione, 3-methyl-6,7-methylenedioxy-3,4-dihydroisoquinolin-1(2H)-one, 2-methyl-(6,7-methylenedioxyphenyl)-3-methylmorpholine and N-cyclohexylacetamide (structure A8) are important contaminants in 3,4-MDP-2-P. It was acknowledged that the latter amide is route-specific only in the particular case when acetic acid and cyclohexylamine are used in the condensation; replacement of the amine with others would yield other amides. Origins of the isoquinolinoline, the isoquinolininedione and the morpholine were not discussed.

A less common synthetic process for the production of 3,4-MDP-2-P is the Wacker reaction [41]. In this process safrone is treated with palladium chloride and methanol in the presence of p-benzoquinone to yield the ketone (Fig. 2). In a study conducted by Cox and Klass [10], it was found that 1-(3,4-methylenedioxyphenyl)-1-methoxypropan-2-one (structure G1), methyl-3-(3,4-ethylenedioxy-3,4-dihydroisoquinolin-1(2H)-one, 2-methyl-(6,7-methylenedioxyphenyl)-3-methylmorpholine and N-cyclohexylacetamide (structure A8) are important contaminants in 3,4-MDP-2-P. It was acknowledged that the latter amide is route-specific only in the particular case when acetic acid and cyclohexylamine are used in the condensation; replacement of the amine with others would yield other amides. Origins of the isoquinolinoline, the isoquinolininedione and the morpholine were not discussed.

4. Characteristic ATS impurities, intermediates and by-products

4.1. Methylamphetamine (MA)

Methylamphetamine remains, by far, the most widely manufactured ATS worldwide [42]. Several articles describe the most
common synthetic methods employed in the manufacture of MA, the precursor materials used and the reaction markers associated with these syntheses [43–50]. The multitude of synthetic pathways utilised in the manufacture of MA are summarised in Fig. 1.

The most popular synthetic routes employed by clandestine laboratories in Australia are the iodine/phosphorus methods (Fig. 1) [31,51] with the Birch reduction of lesser prominence [31,52]. It has been reported that nearly all MA produced in the USA is prepared by one of two methods, either from P-2-P with the mercury amalgam reductive amination method or from the reduction of ephedrine or pseudoephedrine. With P-2-P scheduled in the USA and in other parts of the world as a schedule II drug, syntheses tend towards the use of ephedrine or pseudoephedrine as precursor materials. However, with the recent increased restrictions on the sale of ephedrine/pseudoephedrine there may be a resurgence of the synthetic methods utilising P-2-P. The main synthetic routes of MA manufacture in Europe have been reported as being reductive amination and the Leuckart route [43–48].

4.1. The Nagai, “Moscow” and “Hypo” methods

Discussions of the mechanism of the Nagai preparation of MA from ephedrine or pseudoephedrine and its stereochemistry can be found in references [18–21]. In short, the hydroxyl group in the starting material undergoes nucleophilic substitution with iodide to form either iodoephedrine or iodopseudoephedrine. In both of these intermediates iodide can be displaced by internal nucleophilic attack from the adjacent nitrogen to form cis- and trans-1,2-dimethyl-3-phenylaziridines. These aziridines can undergo two reactions: reduction to yield MA; and hydrolysis to yield P-2-P. Under the acidic conditions P-2-P can undergo condensation to yield 1,3-dimethyl-2-phenyl-naphthalene and 1-benzyl-3-methyl-naphthalene. Of this multitude of possible by-products only the two naphthalenes are reported to be route specific. However, it is important to bear in mind that the naphthalene arises simply because P-2-P has been heated in the presence of acid for a length of time and other conditions that duplicate these could also lead to the formation of the naphthalenes.

The important feature of the Nagai reaction is that nucleophilic attack never takes place on the carbon atom in the 2-position on the propane chain, therefore the configuration about that centre (S)-is preserved and the potent d-MA is exclusively formed. Barker and Antia [24] subjected methylephedrine, methylpseudoephedrine, norephedrine and norpseudoephedrine to the Nagai, “Moscow” and “Hypo” methods. The desmethyl compounds reacted as expected to produce cis- and trans-3-phenyl-2-benzylmethylketimine from the condensation between P-2-P and amphetamine. As expected, methylephedrine and methylpseudoephedrine reduced to yield DMA (Fig. 5), but in addition 1-propenylbenzene and 2-propenylbenzene were detected (as indicated below, these olefins are also produced in the Emde reaction of methylephedrine and methylpseudoephedrine).

Iodoephedrine (structure B2), iodopseudoephedrine and the aziridines are all vulnerable to nucleophilic attack and MA can act as a nucleophile. It is therefore not surprising that the “methylamphetamine dimer” is found as a by-product of the Nagai reaction; Tanaka [53] was the first to identify this compound. Windahl et al. [21] also examined the Nagai method. They were not able to find the dimer reported by Tanaka but identified the presence of N-methyl-N-(α-methylphenyl)-amino-1-phenyl-2-propanone (Fig. 6, structure B3) and cis-cinnamoyl MA (structure B1), with the structures confirmed by independent synthesis. Windahl et al. did not conjecture as to how B3 or B1 form but did provide evidence to indicate that they arise from reaction between 1,2-dimethyl-3-phenylaziridine and MA. Iodoephedrine (structure B2) is also considered a characteristic marker compound for MA produced via the Nagai method.

Ko et al. [6] examined a modified Nagai preparation of MA (using red phosphorus and hydrochloric acid). Although they did not detect the aziridines, they did detect 1-phenyl-2-propanone, N-formylmethylamphetamine, N-acetylmethylamphetamine, 1,3-dimethyl-2-phenyl-naphthalene, 1-benzyl-3-methyl-naphthalene, N-methyl-N-(α-methylphenethyl)amino-1-phenyl-2-propane (structure B3) and (Z)-N-methyl-N-(α-methylphenethyl)-3-phenylpropanamide (structure B4).

4.1.2. The Emde method

The Emde method has been found to be the most widely used method in large-scale syntheses in South East Asia in the production of MA [54]. The Emde method proceeds via a pathway similar to the Nagai method inasmuch as ephedrine or pseudoephedrine are halogenated and then hydrogenated with preservation of the stereochemistry around the carbon bearing nitrogen. One difference in the Emde method, however, is that hydroxyl in the starting material can be replaced by chloride via either intramolecular nucleophilic displacement (a so-called S_N2 substitution) or intermolecular displacement (S_N2 substitution). The work of Lekskulchai et al. [55] and Allen and Kiser [56] are at variance in regards to the relative contributions of the two pathways when thionyl chloride is used. Allen and Kiser indicate that (−)-ephedrine yields a 99:1 mixture of (+)-chloropseudoephedrine and (−)-chloroephedrine and that (+)-pseudoephedrine yields a 60:40 mixture whereas Lekskulchai et al. report no difference in the products of chlorination of (+)-pseudoephedrine and (−)-ephedrine (approximately 50:50 mixtures of the chlorides). Barker and Antia [24], in their examination of the Emde reaction applied to extracts of Ephedra, agreed with Allen and Kiser and, through examination of the chlorination products of (−)-norpseudoephedrine, (−)-methylpseudoephedrine and (−)-methylpseudoephedrine, established that the S_N2 substitution reaction becomes more dominant as the level of methylation on the nitrogen atom increases. Both Allen and Kiser [56] and Barker and Antia [24] used nuclear magnetic resonance spectroscopy (NMR) and gas chromatography–mass spectrometry (GC–MS) to analyse reaction products. It was found that the higher temperature used in GC–MS encouraged the chlorinated products to ring-close and produce mixtures containing 1,2-dimethyl-3-phenylaziridines. As (+)-pseudoephedrine yields a mixture of (+)-chloropseudoephedrine and (−)-chloroephedrine and (−)-ephedrine yields essentially pure (+)-chloropseudoephedrine, and as GC–MS causes (+)-chloropseudoephedrine to cyclise to cis-1,2-dimethyl-3-phenylaziridines and (−)-chloroephedrine to cyclise to trans-1,2-dimethyl-3-phenylaziridines, GC–MS analysis can be used to infer whether (+)-pseudoephedrine or (−)-ephedrine starting material was used. As (+)-norpseudoephedrine and (−)-norephedrine chlorinate to yield similar mixtures of the chlorides and neither (+)-chloromethylpseudoephedrine nor (−)-chloromethylpseudoephedrine can cyclise to yield aziridines, GC–MS cannot be used to infer the identity of the starting material in these cases [24]. GC–MS analysis was found by Barker and Antia to cause (+)-chloromethylpseudoephedrine and (−)-chloromethylpseudoephedrine to eliminate HCl and produce 1-propenylbenzene and 2-propenylbenzene and to rearrange to produce 1-dimethylamino-1-phenyl-2-chloropropane (tentative identifications). Ko et al. [6] examined the Emde method for the production of MA. In addition to the aziridines they detected trace amounts of two unidentified compounds one with a base peak at 120 Da and one with a molecular weight of 239 Da. The former was present in all chloroephedrine samples and therefore was felt to be an important contaminant but the authors did not rule out the possibility of it being a GC injection artefact. The latter was reported to be a
Fig. 6. Characteristic contaminants in the manufacture of MA by synthetic routes: Reductive amination (A1–A4); Nagai method (B1–B4); Emde method (C1–C6); Birch method (D1); Leuckart method (F1–F3).
contaminant arising, by means unknown, from the hydrolysis step. In later work, Ko et al. [57] identified the injection artefact to be 1-methylamino-1-phenyl-2-chloropropane, which is produced by vapour-phase nucleophilic attack of chloride upon the aziridine. They also confirmed that the identity of the other unknown was N-methyl-1-(4-(2-(methylamino)propyl)phenyl)-1-phenylpropan-2-amine, as reported by Salouros et al. [58]. The conclusion drawn by Ko et al. was that the presence of aziridines in mixtures cannot be used to differentiate between the involvement of the Nagai or Emde methods; 1-methylamino-1-phenyl-2-chloropropane (chloroepinephrine/chloropseudoephedrine, structure C1) on the other hand is route-specific for the Emde process. Compounds C2–C6 are also produced by the Emde method.

As indicated above, Salouros et al. [58] identified N-methyl-1-(4-(2-(methylamino)propyl)phenyl)-1-phenylpropan-2-amine in MA prepared using the Emde route and also detected two isomers of N-dimethyl-3,4-diphenylhexane-2,5-diamine. The identity of both of these compounds was verified by independent synthesis. In agreement with Lee et al. [7] and Ko et al. [6], Salouros et al. [58] et al. also detected N-methyl-1-(4-(2-(methylamino)propyl)phenyl)-1-phenylpropan-2-amine in material produced by the “Moscow” and Nagai methods, therefore this amine is not route specific. The origin of N-dimethyl-3,4-diphenylhexane-2,5-diamine and N-methyl-1-(4-(2-(methylamino)propyl)phenyl)-1-phenylpropan-2-amine is the bond of chloropseudoephedrine or chloropseudoephedrine by hydrogen atoms to form a delocalised radical that can either pick up a hydrogen atom to form MA or dimerise through the benzylic position to form N-dimethyl-3,4-diphenylhexane-2,5-diamine or through the para position to form N-methyl-1-(4-(2-(methylamino)propyl)phenyl)-1-phenylpropan-2-amine [58].

1.3. The Leuckart method

In the preparation of MA by the Leuckart method the key intermediate is N-formylmethylamphetamine. Kram and Kruegel [59] indicate that N,N-di-(β-phenylisopropyl)methyamine and N-formylmethylamphetamine are encountered in illicit MA prepared by the Leuckart reaction; it was suggested that the former might not be route-specific while the latter is. Sanger et al. [60] have written that N-formylmethylamphetamine is route-specific for the Leuckart reaction and this is unequivocal if substantial quantities of that amide are present. However, Qi et al. [61] and groups after them [53,32] have evidence that N-formylmethylamphetamine is found, albeit at very low levels, in MA synthesised by methods other than the Leuckart. Qi et al. found that the presence of N-formylmethylamphetamine was correlated with the presence of N-acylmetnamphetamine, which in turn was said to have arisen from reaction between MA and ethyl acetate. Several years before Qi et al. detected N-acylmetnamphetamine, Conn et al. [62] were the first to document its presence in illicit MA and attributed its presence to the usage of propylacetate to azetropically desiccate MA that had been salted-out using aqueous hydrochloric acid. Sasaki and Makino [63] indicate that the abundance of both N-formyl- and N-acyl-metnamphetamine increases with increasing injection port temperature and surmised that they arise from thermal decomposition of an unknown compound (or compounds) that are seen to decrease with increasing temperature. In any event, the presence of N-formylmethylamphetamine at the trace level in illicit MA might require cautious interpretation.

Kram and Kruegel [64] also report that a compound of MW 239 Da, tentatively identified as N-methyldiphenylethylamine, was detected in illicit MA produced by the Leuckart reaction. In a later article Kram [65] indicates that the actual identity of this compound was di-(1-phenylisopropyl)formamide.

Unlike the situation when the Leuckart method is used for the production of primary amphetamines, where condensations involving formamide lead to the production of a multitude of heterocyclic by-products (see below), side reactions leading to analogous heterocycles cannot take place in the Leuckart preparation of MA because the N-methyl group effectively blocks them [66].

Kunalan et al. [5] compared by-products from the Leuckart preparation of MA with those from a reductive amination and concluded that α,α′-dimethylphenylethylamine (structure F2) and N-α,α′-trimethylphenylethylamine (structure F3), in this context at least, are route-specific for the Leuckart reaction.

If impure P-2-P, methylamine, or N-methylformamide (which may contain dibenzylketone, ammonia and formamide, respectively) are used in the Leuckart reaction then α-benzylphenethyline, N-formyl-α-benzylphenethyline, α-benzyl-N-methylphenethyline (structure F1), amphetamine and formylamphetamine impurities can be detected in MA [50,59]. In addition to the above, Kunulan [5] detected in MA prepared by the Leuckart method the presence of bibenzyl, 3,4-diphenyl-3-butene, benzylmethamphetamine, N-β-(phenylisopropyl)benzyl methyl ketimine, N-benzylmethamphetamine, benzylamphetamine, N-benzoylamphetamine, and several pyridines associated with the Leuckart preparation of AP (the latter desmethylated by-products were presumed to have arisen from the presence of formamide in the N-methylformamide used in the reaction).

1.4. The Birch reduction

Although the chemistry involved in the Birch reduction of ephedrine or pseudoephedrine is somewhat exotic, there is only one major contaminant in the final product reported: 1-(1,4-cyclohexadienyl)-2-methylaminopropane (structure D1) [8]. If the starting material is not pure then other materials can undergo reduction as well. Barker and Antia [24] describe the situation when extracts of plants of the genus Ephedra are used as starting material. The methyl and desmethyl analogues of ephedrine and pseudoephedrine (e.g. methylephedrine and norephedrine) are reduced, as expected, to AP and DMA and the main by-products are desmethyl and methyl analogues of 1,4-cyclohexadienyl-2-methylaminopropane (structures D2 and D3, not confirmed by independent synthesis). As might be expected, the 1,4-cyclohexadienyl moiety in 1-(1,4-cyclohexadienyl)-2-methylaminopropane (and presumably its analogues D2 and D3) is prone to aromatisation to form MA. Pal et al. [67,68] report that this aromatisation takes place rapidly in soil, chiefly by processes that do not involve microorganisms. The implication is that residues from clandestine laboratories, especially those retrieved from soil but also those that might have had sufficient time and appropriate conditions to oxidise, might not contain 1-(1,4-cyclohexadienyl)-2-methylaminopropane even if it was once there. Similarly, the presence of MA might be due to oxidation of the diene rather than it being initially present in the residue.

1.5. Reductive amidation

Verweij [50] reviewed the reductive aminations of P-2-P in the presence of both ammonia and methylamine and cites his own earlier publication in German. A by-product, common to both not surprisingly, was 1-phenyl-2-propanol (structure A1), which arises from the reduction of starting ketone. The alcohol was reported to be a route-specific by-product.

In a paper dealing chiefly with the reductive amination of 3,4-MDP-2-P, Salouros et al. [69] mention in passing that the reductive amination of P-2-P with methylamine produces the by-product N-cyanomethyl-N-methyl-1-phenyl-2-propylamine (structure A4), which is likely to be route-specific.

Kunalan et al. [5] compared the contaminants in MA prepared by the Leuckart and reductive amimation routes. They confirmed the finding by Verweij [50] that 1-phenyl-2-propanol was a...
route-specific by-product of their reductive amination (methylamine in the presence of amalgamated aluminium in methanol). They also reported that 1-phenyl-2-propanol was not recovered by extraction of the reaction mixture at basic pH. Kunulan et al. also report many other contaminants detected in the reductive amination product that were also present in the Leuckart reaction mixture such as AP, DMA (that could have arisen from impurities in methylamine) and their formyl, benzoyl and benzyl derivatives, bibenzyl and pyridines.

4.1.6. Impurities found in seizures

Many articles deal with the analysis of seized MA where it is not known exactly which particular method might have been used in manufacture or even if the seizures actually contain material from more than one batch or method. Many of these articles deal more with developing processes for comparing seizures rather than proving the identity and origin of the contaminants.

Impurities such as AP (structure A2), DMA and P-2-P were among the first to be described as commonly occurring in illegal MA [39] suspected to have been produced by the Leuckart reaction. AP has also been seen in illicit MA preparations via the reductive amination route.

In a study conducted by Puthaviriyakorn et al. [70] ten contaminants were identified in “Ya Ba” tablets. These compounds are 1,2-dimethyl-3-phenylaziridine, ephedrine, methylephedrine, N-formylmethamphetamine, N-acetyl-methamphetamine, N-formylephedrine, N-acetylmethedrine, N.O-diacetylmethedrine, methamphetamine dimer and a newly identified impurity trans-3,4-dimethyl-5-phenyl-2-oxazolidone. The “dimer” was first reported by Tanaka [53], who identified it in MA seized in Japan.

Dayrit and Dumlao [71] found MA samples suspected to be synthesised by the Leuckart method to contain the impurities p-bromotoluene, N-benzylamphetamine, N-ethylmethamphetamine, N-ethylamphetamine as well as P-2-P, DMA, and N-formylamphetafine.

N-benzylamphetamine has been reported [61,72] to be an impurity in illicit MA but its origin is obscure.

Between 1998 and 2002, the Australian Federal Police seized and analysed 19 crystalline MA ‘ice’ samples [73] and found 36 separate contaminants, six of which could not be identified. Of note were the presence of 1-phenyl-2-propanol (Fig. 6, structure A1), which is indicative of these samples being synthesised via the reductive amination route, benzyl chloride, bibenzyl and benzyl alcohol.

4.2. 3,4-Methylenedioxyamphetamine (MDMA)

4.2.1. The Leuckart method

Verweij [49] reviewed three methods for the production of MDMA and MDA: the Leuckart reaction; reductive amination; and the bromopropone route (a route not discussed herein). Unfortunately only the production of MDA was discussed with regards to the Leuckart route and Verweij indicated that N-formyl-MDA was a route specific by-product. He also reported upon the presence of di-[1-(3,4-methylenedioxy)phenyl-2-propyl]amine (MDMA dimer), an expected by-product, and di-[1-(3,4-methylenedioxy)phenyl-2-propyl]methylamine (MDMA dimer, Fig. 7, structure A11) an unexpected contaminant, presumably arising from N,N-dimethylformamide impurity in the formamide used. Additional compounds, also presumably impurities rather than by-products, were safrrole, isosafrole, 1,2-(methylenedioxy)-4-propylbenzene and isosafrole glycol.

Renton et al. [74] reported that the only contaminant in MDMA prepared by the N-methylformamide/formic acid reaction was N,N-dimethyl-3,4-MDA, which presumably arises as a result of N,N-dimethylformamide impurity in the N-methylformamide.

Surprisingly, in the same article while discussing the Leuckart formation of MDMA in boiling N-methylformamide, Renton et al. tentatively identified the 3,4-methylenedioxy pyridine (3,4-bis-(1,3-benzodioxol-5-ylmethyl)pyridine, structure F10) and pyrimidine (5-(1,3-benzodioxol-5-ylmethyl)pyrimidine, structure F9). Whether this was due to a demethylation step during condensation or as a result of formamide impurity in N-methylformamide was not discussed.

Cheng et al. [75] reported on tablets containing MDMA thought to be prepared by the Leuckart method. Their findings mirror those of Verweij [49] above in that dimers, pyridines and 4-methyl-5-(3,4-methylenedioxyphenyl)pyrimidine were detected (tentatively). However, in this instance, because the drug present was MDMA rather than MDA, the expected by-product was the MDMA dimer (structure A11) and the pyridines, the pyrimidine and MDA dimer were unexpected products.

As discussed in the next section, both Swist et al. [36] and Cheng et al. [75] have some evidence that N-formyl-MDMA (structure F8) is associated with the synthesis of MDMA via reductive aminations as well as via the Leuckart reaction. Compounds F4–F7 have also been identified as route-specific markers in MDMA production via this route.

4.2.2. Reductive amination

Verweij [76] examined reductive amination of 3,4-MDP-2-P using aluminium amalgam and methylamine in boiling ethanol and identified 12 contaminants in the final product. One of these, 3,4-MDP-2-propanol, is a reaction-by-product and another, 1,2-(methylenedioxy)-4-(2-N-methyliminopropyl)benzene (structure A9), is the reaction intermediate. The other 10 compounds included MDA, N,N-dimethylMDA, N-methyl-N-ethylMDA (originating from impurities in methylamine), safrrole and isosafrole, the hydrogenation product of safrrole (1,2-(methylenedioxy)-4-propylbenzene), 1,2-(dimethoxy)-4-propenylbenzene, 3,4-methylenedioxybenzaldehyde and 1,2-(methylenedioxy)-4-methylbenzene all of which would have been contaminants in the 3,4-MDP-2-P starting material. In a later review [49], Verweij also indicates that 3,4-(methylenedioxy)benzyl-N-methylamine is present in the reductive amination product.

Other common reductive aminations for the production of MDMA involve the use of sodium borohydride (NaBH₄) or sodium cyanoborohydride as the reducing agent (Fig. 2) [77], Swist et al. [78] prepared MDMA salt using all three of the above reductive aminations (and the Leuckart reaction) and examined the contaminants that could be extracted from the salt under basic conditions. The authors concluded that 1,2-(methylenedioxy)-4-(2-N-methyliminopropyl)benzene (structure A9) is a route specific by-product for the three reductive aminations but also noted that it might not be present if the reduction has been efficient. Also detected were 3,4-(methylenedioxy)benzyl-N-methylamine, 3,4-(methylenedioxy)benzyl-N,N-dimethylamine, N-(3′,4′-methylene-dioxybenzylo)MDMA and N-methyl-2-methoxy-1-methyl-2-(3,4-methylenedioxyphenyl)-ethaneimine (structure A7, this being an impurity carried through from 3,4-MDP-2-P prepared from isosafrole by oxidation). These compounds were also detected in the Leuckart preparation. It was also suggested by Swist et al. [78] that 2-(dimethylinamo)-2-methyl-3-(3,4-methylenedioxyphenyl)-propanenitrile is a route-specific by-product in the sodium cyanoborohydride reductive amination but later work by Salourou et al. [59] unambiguously identified this by-product as N-cyanomethyl-N-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine (structure A10).

In slightly later work [77] Swist et al. examined basic and neutral impurities extracted from MDMA salt prepared using the three reductive amination methods. In addition to the compounds listed above in this work Swist et al. also reported the presence of
3,4-methylenedioxyphenyl-2-propanol but only in reductions conducted using sodium borohydride. When 3,4-MDP-2-P was prepared from 3,4-methylenedioxybenzaldehyde via the nitrostyrene 3-methyl-6,7-methylenedioxyisouquinoline-1,4-dione, N-cyclohexylacetamide and 5-(3',4'-methylenedioxyphenyl)-3,4-dimethyloxazolidinone impurities were detected. As indicated above, this particular amide only arises when cyclohexylamine is used to catalyse the formation of the nitrostyrene. It was indicated that extraction under basic conditions was much more effective than extraction under neutral conditions.

Fig. 7. Characteristic contaminants in the manufacture of MDMA by synthetic routes: Reductive amination (A5–A11); Leuckart route (F4–F10); "Wacker" oxidation (G1–G5); Peracid oxidation (H1–H6).
Gimeno et al. [35] also examined contaminants arising from the three reductive aminations. In addition to the compounds described previously by Verweij et al. [49], Gimeno et al. also detected 1,3-benzodioxazole, PMA, 3,4-(methylenedioxy)benzyl alcohol and 3,4-(methylenedioxy)benzyl chloride. As indicated above, Gimeno et al. also report the presence of 3,4-dimethoxy-y-methylamphetamine (which they call “Smeth”) but published an incorrect structure for that compound. Gimeno et al. concluded that it was not possible to use contaminant profiles to deduce which of the three reductive amination methods were used in the preparation of MDMA.

4.2.3. Impurities found in seizures

An impurity found in MDMA samples seized and analysed in France was N-formyl-MDMA (structure F8). This impurity, present in 25% of the samples is said to be specific to the Leuckart reaction [79]. In addition to the compounds discussed above, ketamine, DMA, 3,4-methylenedioxybenzaldehyde, PMA, 3,4-methylenedioxybenzyl alcohol and 3,4-methylenedioxyethylamphetamine have been detected and used for profiling, however they are not specific to a particular synthetic route.

Gimeno et al. [80] profiled 10 MDMA seizures and identified (presumably by mass spectrometry alone) 26 different compounds of which benzaldehyde, 1,3-benzodioxole, 3,4-methylenedioxytoluene, AP, 1,2-dimethyl-3-phenylaziridine, safrole, 3,4-methylenedioxyphenyl propane, 3,4-methylenedioxybenzaldehyde, methycathine, 3,4-dimethoxybenzyl chloride, isosafrole, 3,4-methylenedioxy-N-methylbenzylamine (structure A5), 3,4-methylenedioxy-N,N-dimethylaniline, 3,4-methylenedioxybenzyl alcohol, PMA 3,4-methylenedioxy-N-ethyl-N-methylamphetamine, N,N-dimethoxy-(1,2-dimethoxy-4-(2-aminopropl)benzene, N-methyl-1-[1,2-dimethoxy-4-(2-aminopropl)benzene, N-ethyl-N-methyl-1,2-dimethoxy-4-(2-aminopropl)benzene and N-methyl-(1,2-dimethoxy)-4-(1-ethyl-2-aminopropl)benzene can be classified as impurities arising from various sources. This article includes a wealth of mass spectral data.

4.3. Amphetamine (AP)

4.3.1. The Leuckart method

Due to its simplicity, the Leuckart reaction is the preferred synthetic route employed for the illicit manufacture of AP [81]. As the Leuckart preparation of AP involves the production of N-formylamphetamine as an intermediate, the latter can be encountered in the final product if hydrolysis is incomplete [60]. As indicated by Blachut [82], if formamide is used in the Leuckart preparation then condensations can occur between it and P-2-P to yield a number of route-specific heterocyclic by-products. The first mention of these was by Sinnema and Verweij [83] who tentatively identified five pyridines, one pyridone and two pyrimidines. Later the structures of the pyrimidines (4-methyl-5-pyrimidinylidine and 4-benzopyrimidylidine) [84] and two pyridines (2,4-dimethyl-3,5-diphenylpyridine and 2,6-dimethyl-3,5-diphenylpyridine) [82] were unambiguously assigned (structure F12–F15). As formamide can be contaminated with N-methylformamide the product of Leuckart preparation of AP can also include MA but this impurity is not route specific. Similarly, if P-2-P contaminated with dibenzylketone is used in the Leuckart reaction then α-benzylphenethylamine [85] and α-benzylphenylethylamineformamide (Fig. 8, structure F11) [65] will be formed, the latter being route-specific but the former not.

4.3.2. Nagai. “Moscow”, “Hyp0”, Emde and Birch methods

In a study conducted by Barker and Anita [24], six main marker compounds were identified in the synthesis of AP from norephedrine/norpseudoephedrine via the Nagai route (hydrogen iodide and red phosphorus). The six by-products were cis- and trans-2-methyl-3-phenylaziridine, P-2-P, 1,3-dimethyl-2-phenylaziridine, 1-benzyl-3-methylphenylthaleine, and N-(β-phenylisopropyl) benzyl methyl ketamine. By-products resulting from the metal catalysed hydrogenation of norephedrine/norpseudoephedrine (the Emde method) in the production of AP closely parallel those found in the manufacture of MA. The by-products identified for AP include chloronorpseudoephedrine/chloronorephedrine (structure C7), and cis- and trans-2-methyl-3-phenylaziridine [24]. Although both the Emde and Nagai (and related) methods produce the same aziridines as by-products it is not correct to infer that illicit material containing them must have originated from one of these two methods. Reduction of P-2-P ketoxime by lithium aluminium hydride, for example, also produces these aziridines [86].

The Birch reduction of norephedrine/norpseudoephedrine to form AP gives rise to one characteristic marker, 1-[(1,4-cyclohexadienyl)-aminopropane (Fig. 8, structure D2), as described by Barker and Anita [24].

4.3.3. Reductive amination

The presence of the compounds (2-nitroprop-1-enyl)benzene (structure I1), benzyl methyl ketoxime (structure D2), N-(β-phenylisopropyl) benzaldehyde (structure I3), and 2-methyl-3-phenylaziridine [43] in a sample may be indicative of the “Nitrotryline” route being employed in the conversion of P-2-P to AP (Fig. 8).

Theeuwen and Verweij [87] identified unambiguously the presence of benzyl methyl ketone phenylisopropylamine and benzyl methyl ketone benzylamine by-products in the reductive amination of P-2-P using ammonia, Raney nickel and hydrogen. The authors surmised that the by-products are detected only when hydrogenation is incomplete and the water that is produced by condensation side-reactions is removed from the reaction mixture. These imines arise as a result of condensation between AP and P-2-P and AP and benzaldehyde, respectively. Although N,N-di-(β-phenylisopropyl)amine (the hydrogenated product of benzyl methyl ketone phenylisopropylamine) is commonly detected in illicit AP [83], the corresponding product of hydrogenation of benzyl methyl ketone benzylamine (i.e. N-benzylamphetamine) is not. Possibly this compound undergoes hydrogenolysis under the reaction conditions to yield AP and 1-phenylpropane. Allen and Cantrell [26] indicate that if an excess of ammonia is not used in the reductive amination then a competing side-reaction, reduction of P-2-P, takes place with the production of phenyl-2-propanol. Verweij [50] indicates that other by-products and impurities found in illicit AP prepared by reductive amination are N-acetylamphetamine (origin not explained) and dibenzyl ketone (presumably arising from contaminated P-2-P). Huizer et al. [88] report that reductive amination using ammonia and ammonium chloride yielded a thermally labile by-product (tentatively identified as 2,4-dihydroxy-1,5-diphenyl-4-methylenepent-1-ene) that decomposed into cis- and trans-1,5-diphenyl-2-methyl-4-oxopent-1-ene and cis- and trans-1,5-diphenyl-2-methyl-4-oxopent-2-ene. In addition, the presence of 3,4-dihydro-2-benzyl-2-methyl-4-oxo-5-phenyl-2-hyprolate was tentatively identified at a trace level. With the possible exception of these latter olefins and the pyrrole, which surprisingly do not appear to have been detected in any other synthetic pathways to AP from P-2-P, none of the above compounds can be considered to be route-specific for the reductive amination of P-2-P.

4.3.4. Impurities found in seizures

Nevescani et al. [72] reported that N-benzylamphetamine together with many of the compounds listed above were detected in AP seized in Serbia. Although the origin of this amide was not discussed it could be an impurity arising from the reaction
between AP and benzoic acid (itself an impurity in benzaldehyde). Other impurities that have been identified in AP samples include N-benzylamphetamine, N,N-di-(β-phenylisopropyl)methylamine, 1,3-diphenyl-2-propylamine, 4-benzylpyrimidine, N-formylamphetamine, N,N-di-(β-phenylisopropyl)amine, N,N-di-(β-phenylisopropyl)formamide, and 2,4-dimethyl-3,5-diphenylpyridine [43,61,84,89].

4.4. N,N-Dimethylamphetamine (DMA)

The precursor chemicals commonly employed in the production of DMA are methylephedrine and methylpseudoe

![Chemical structures]

**Fig. 8.** Characteristic contaminants in the manufacture of AP by synthetic routes: Emde route (C7); Birch reduction (D2); Leuckart route (F11); Nitrostyrene route (I1–I3).

**Fig. 9.** Characteristic contaminants in the manufacture of DMA by synthetic routes: Nagai method (B5–B6); Emde (C8–C9); Birch reduction (D3).
The Birch reduction of methylephedrine or methylpseudoephedrine to DMA commonly results in one characteristic compound, 1-(1′,4′-cyclohexadienyl)-2,2-dimethylaminopropane (Fig. 9, structure D3) [24].

4.5. p-Methoxyamphetamine (PMA)

The only synthesis of PMA to be described in the literature is the Leuckart preparation from PMP-2-P, 4-methyl-5-(4-methoxyphenyl)pyridine (Fig. 10, structure F17) and 4-(4-methoxybenzyl)pyrimidine (structure F16) were unambiguously identified as by-products in the Leuckart preparation of PMA [84] and, as they are derived from the condensation between formamide and PMP-2-P, are likely to be route-specific for the Leuckart preparation. Blachut et al. [90] detected these two pyrimidines and tentatively identified the presence of at least six pyridines of molecular weight 319 or 333 Da in crude products from the reaction. In later work the same authors [82] positively identified two pyridines with molecular weight 319 Da, namely 2,4-dimethyl-3,5-di-(4′-methoxyphenyl)pyridine and 2,6-dimethyl-3,5-di-(4′-methoxyphenyl)pyridine (structures F18–F19). It was found that the presence of these pyridines at significant levels was indicative of the use of formamide in the reaction mixture rather than ammonium formate and furthermore it was found that abundant 2,6-dimethyl-3,5-di-(4′-methoxyphenyl)pyridine compared to 2,4-dimethyl-3,5-di-(4′-methoxyphenyl)pyridine indicated that formic acid was present.

In a manner analogous to that observed for the production of AP by the Leuckart reaction the imine by-products and their reduction products N-(β-4-methoxyphenylisopropyl)-4-methoxybenzyl methyl ketimine, 1-(4-methoxyphenyl)-N-(2-(4-methoxyphenyl)-1-methylethyl-2-propanamine and N-(β-4-methoxyphenylisopropyl)-4-methoxybenzaldimine are detected in the Leuckart synthesis of PMA but as they arise from the condensation of PMA and PMP-2-P they are therefore not route-specific by-products.

In regards to impurities found in illicit PMA preparations, Coumbaros et al. [39] detected the two route-specific pyrimidines and 4-methoxyphenol (Fig. 10, structure H7) the origin of which, as described earlier, was found to be the Bayer-Villiger oxidation of 4-methoxybenzaldehyde present in the anise oil starting material [38]. Coumbaros et al. also tentatively identified the presence of 4-methoxyphenyl-2-propanol, which was likely to have originated from PMP-2-P. Blachut et al. [90] also reported the presence of 4-hydroxymethamphetamine, N,N-dimethylPMA and N-ethylPMA in illicit tablets.

5. Summary

It is not uncommon to see different synthetic routes sharing the same by-product formation. One common by-product, P-2-P, is sometimes thought to be a ‘characteristic’ marker, however, due to its presence as a by-product in multiple reactions or even as unreacted precursor, it should be classified as a “common” by-product. P-2-P is found in MA synthesised via reductive amination and the Nagai method, also in MDMA synthesised via the Leuckart reaction and in AP and DMA synthesised via the Nagai method.

Similarly, cis- and trans-1,2-dimethyl-3-phenylaziridine are common by-products of MA synthesised via the Nagai method and also the Emde method. The by-product N-(β-phenylisopropyl) benzyl methyl ketimine has been described as a characteristic by-product in the production of AP via reductive amination [61]. However, it has also been found in the synthesis of AP via the Nagai method, suggesting that this marker compound is not characteristic to the reductive amination method. 1,3-Dimethyl-2-phenyl-naphthalene has been reported as a by-product in the production of MA and AP via the Nagai method.

Table 1 summarises the characteristic contaminants resulting from the manufacture of MA, MDMA, AP, DMA and PMA (Figs. 6–10 that provide the chemical structures of the characteristic contaminants for each ATS). It is evident that the number of characteristic by-products varies amongst different synthetic routes and also amongst different drug compounds. This can be explained by the nature of the synthetic route itself, since the varying reaction pathways may have a greater or lesser likelihood of by-products resulting. However, a more logical explanation could be that the most common synthetic routes, i.e. reductive amination and the Leuckart methods, are the most frequently used and thus the most researched methods, which in turn leads to the determination and identification of the greatest number of

![Fig. 10. Characteristic contaminants in the manufacture of PMA by synthetic routes: Leuckart method (F12–F13); Peracid oxidation (H7).](image-url)
characteristic by-products. This suggests that further research is needed in the area of profiling and drug intelligence.

By-product and impurity profiling can be a very useful tool in identifying the method of manufacture; however, great care must be taken in interpreting the significance of by-products and impurities present in an illicit sample. Marker compounds are of most significance when accurately identifying the synthetic method; i.e. when they are route-specific or precursor-specific. With this knowledge in mind, it is possible to achieve great discrimination in identifying these ATS and the different precursors used and the synthetic routes of manufacture.

6. Adulterants and cutting agents

Adulterants are added to illicit drugs in order to modify the physiological properties of preparations. Cutting agents can be inert substances that are added solely to increase product bulk. Some common adulterants and cutting agents used in the production of MA and other ATS include dimethysulfoxine, N,N-dimethylamphetamine hydrochloride, ephedrine hydrochloride, sodium thiosulfate, sodium chloride, sodium glutamate, caffeine, sodium benzoate, diphenylhystamine, etyl vanillin and procaine [70,91,92]. MA samples seized in Thailand were also found to contain traces of acetylmethadol, monoacetylmorphine and diacetylmorphine and are thought to have originated from contamination due to MA synthesis overlapping with areas of illicit heroin production [70]. Some common adulterants and cutting agents used in the production of MDMA include caffeine, ketamine, paracetamol, aspirin, dimethylsulfoxine, palmitic acid, stearic acid, atropine and sometimes other amphetamine are also used [79,92,93]. Some common adulterants and cutting agents used in the production of AP include creatine, ephedrine, salicylamide, paracetamol, phenazone and sugar [43]. The presence of adulterants and cutting agents may further aid in discriminating or linking drug samples as some batches may contain the same adulterants and cutting agents, suggesting that they came from the same manufacturer or supplier. Although the presence of common adulterants or cutting agents themselves may suggest a link between seizures, unless a complex or unusual mixture of them is involved, greater evidential value of a link is provided by contaminant profiling. However, assessment of both contaminant and adulterant/cutting agent profiles can be informative. For example, if two seizures exhibit different adulterant/cutting agent profiles yet exhibit identical contaminant profiles the likely situation is that two batches of product were produced using a single source of drug, either from a single clandestine laboratory or from different ones.

7. Intelligence methods

One of the tasks of the European project entitled ‘Collaborative Harmonisation of Methods for Profiling of Amphetamine Type Substances’ (CHAMP) was to develop a harmonised methodology for MA and MDMA profiling and the creation of a common database in a drug intelligence perspective. This project involves two separate parts: Part I includes the analysis of organic impurities formed during synthesis in order to highlight potential links between samples; Part II focuses on physical characteristics of the tablets. Correlation coefficients were used to distinguish between populations of linked samples (from the same seizures) and unlinked samples (from different seizures) [94,95]. Australian efforts in the area of drug profiling are comparatively recent. Following research and development work between 1991 and 1995 the National Heroin Signature Program (NHSW) was established in 1997 [31]. In 2003, the NHSW was expanded to become the Australian Illicit Drug Intelligence Program (AIDIP) [31]. The objective of the AIDIP was to consolidate work completed on heroin and expands into other major drug types. The AIDIP developed signature programmes for heroin, cocaine and the ATS such as MA and MDMA. The AIDIP has two major arms: chemical profiling and physical profiling, which are designed to complement each other. Chemical profiling involves an in-depth chemical analysis of the drugs to provide information that may complement intelligence previously acquired by law enforcement [31].

Aalberg and co-workers [43,44] focused on the development of a harmonised method for the profiling of AP. They synthesised a number of standards i.e. by-products found in illicit AP. Following this they conducted a study focusing on the stability of 22 AP impurities dissolved in six organic solvents in order to find the most inert, and most suitable, solvent for AP profiling. The study proved to be essential due to the fact that unstable compounds can have a negative influence on the comparison of profiles. Anderson et al. [45,46] developed a GC–MS method for the analysis of target compounds found in AP synthesised by the Leuckart method, reductive amination of benzyl methyl ketone, and the “Nitrotryeone” method. Anderson et al. [48] subsequently developed a procedure involving partial least squares discriminant analysis (PLS-DA) to evaluate the effects of various pre-treatment methods on the separation of AP batches synthesised by the Leuckart reaction, reductive amination of benzyl methyl ketone and the “Nitrotryeone” method. A Pearson correlation was applied in order to successfully differentiate AP samples synthesised from different batches.

Dayrit et al. [71] described a GC–MS and gas chromatography–flame ionisation detector (GC–FID) method for the detection and impurity profiling of impurities found in illicit MA samples seized in the Philippines. This method was successful in identifying impurities present in samples synthesised via the Leuckart method. Lee et al. [7] developed a method for the analysis of organic impurities present in MA samples synthesised from ephedrine and pseudoephedrine by the Emde, Nagai and “Moscow” methods using GC–MS and GC–FID. Following a cluster analysis of the characteristic peaks detected, samples were able to be differentiated into four main groups. Tanaka and Inoue et al. [53,99] conducted studies on the impurity profiling of MA seized in Japan using GC. Impurity profiles containing ephedrine and MA dimer were used to establish links between MA seizures.

In 2006, Kuwayama et al. [100] developed a GC–MS method using headspace solid phase microextraction (HS–SPME) for the detection and profiling of impurities in MA samples. MA from nine different origins were analysed and the compounds detected were discriminated by means of logarithmic conversion and cosine distance calculations in order to classify the MA samples into groups. In 2007, a new capillary zone electrophoresis method for the simultaneous chiral determination of the enantiomers of DMA, MA, ephedrine, pseudoephedrine and methylamphetamine (obtained from drug seizures in Hong Kong) was developed [101]. The results suggested that all the samples were not racemic mixtures. This indicated that DMA and MA samples were unlikely to be synthesised through reductive amination of achiral precursor P-2-P, rather DMA and MA in samples were more probably prepared from methylamphetamine and pseudoephedrine or ephedrine, respectively [101]. In 2008, Lee et al. [91] were able to link MA samples seized in Japan to those seized in Korea by means of analysing impurities and additives present in MA seizures using GC–MS and GC–FID. Puthaviyakorn et al. [70] reported GC–MS analysis of MA tablets seized in Thailand. Nine compounds were identified as impurities in the MA samples and these were subjected to multivariate analysis which was successful in characterising and classifying 250 exhibits into five groups. Studies utilising GC–MS for the impurity profiling of MDMA
tablets seized in the Netherlands and Hong Kong have also been reported [75,102].

Another important aspect of drug intelligence is the determination of the enantiomeric purity of a drug. All manufacturing methods starting from L-ephedrine or D-pseudoephedrine produce D-MA as the single product, which is at least twice (in some publications reported to be up to ten times) as potent as the racemic mixture [81]. The identification of an enantiomerically pure sample of MA therefore suggests that L-ephedrine/D-pseudoephedrine was used as starting material, however, a successful attempt at separation of a racemic mixture cannot be ruled-out. If equal amounts of L- and D-MA are present this suggests that P-2-P or some other achiral or racemic compounds were used as the starting material. Some seized samples in Australia have been found to contain unequal amounts of L- and D-MA, which may suggest that two or more samples synthesised from P-2-P, ephedrine or pseudoephedrine have been combined to produce the end product making identification of the route of manufacture complicated. Alternatively, a partially effective enantiomeric purification may have been attempted. In these cases the observation of an unusual mixture of by-products, intermediates or impurities would add weight to the hypothesis that a mixed product is involved.

The source of ephedrine (synthetic/natural) is an important aspect in determining origin of manufacture of a drug. There have been more than 30 different species of Ephedra found, in Europe, Asia and America [24]. However, only a few of these species contain ephedrine related alkaloids at any significant level. Kurashima et al. [96] reported the origin of ephedrine based on the carbon and nitrogen stable isotope ratio values analysed by means of isotope ratio mass spectrometry (IRMS). The various origins of ephedrine (biosynthetic, semi-synthetic derived from molasses, or synthetic) could be discriminated clearly by using these values. In 2009, Kurashima et al. [97] expanded on their previous IRMS work by utilising the hydrogen stable isotope ratio measurement for establishing the origin of ephedrine and pseudoephedrine. The low deuterium content of biosynthetic ephedrines allows a clear distinction from synthetic ephedrines, semi-synthetic ephedrines derived from pyruvic acid and semi-synthetic ephedrines derived from molasses. Matsumoto et al. [98] established a method for the quantitative analysis of the deuterium contents (D/H) at the phenyl, methine, benzyl, N-methyl and methyl groups of L-ephedrine hydrochloride (HCl), D-pseudoephedrine HCl and MA HCl by NMR. By comparison of the 5 position-specific D/H values of L-ephedrine HCl and D-pseudoephedrine HCl prepared by three methods (chemical synthesis, semi-chemical synthesis, and biosynthesis) it was possible to differentiate between chemically synthesised ephedrines and semi-synthetic ephedrines. The classification of several MA samples seized in Japan in terms of the D/H values at these two positions clearly illustrated that the MA samples had been synthesised from biosynthetic or semi-synthetic ephedrines but not from synthetic ephedrine [98].

8. Conclusion

In this review, the contaminants found in MDMA, MA, AP, DMA, and PMA preparations have been described. These contaminants are increasingly important as they are essential in determining possible routes of manufacture and illustrating links between seizures. This review illustrates the large diversity of impurities/intermediates/by-products found in illicit ATS resulting from common synthetic routes and methods in profiling these compounds. The variety of characteristic compounds encountered suggests that significant discrimination between seizures of different origins is possible. Future research is necessary to address knowledge gaps in regards to the manufacture of drugs of current interest, to identify new developments in the synthesis of these drugs (i.e. the identity of new precursors or new synthetic methods) and to develop knowledge in regards to newly emerging drugs.

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.2012.10.040.

References


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