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Forensic analysis of P2P derived amphetamine synthesis impurities: identification and characterization of indene by-products.

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Keywords:	APAAN, alpha-methylstyrene, P2P, impurities, by-products, cyclic indenes
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	regarding the use of APAAN and AMS. Furthermore, the association of these compounds with amphetamine production appears to have been reported for the first time. The presence of compounds **1** – **4** in seized amphetamine samples and waste products could facilitate the suggestion whether APAAN or AMS were employed in the synthesis route to the P2P.

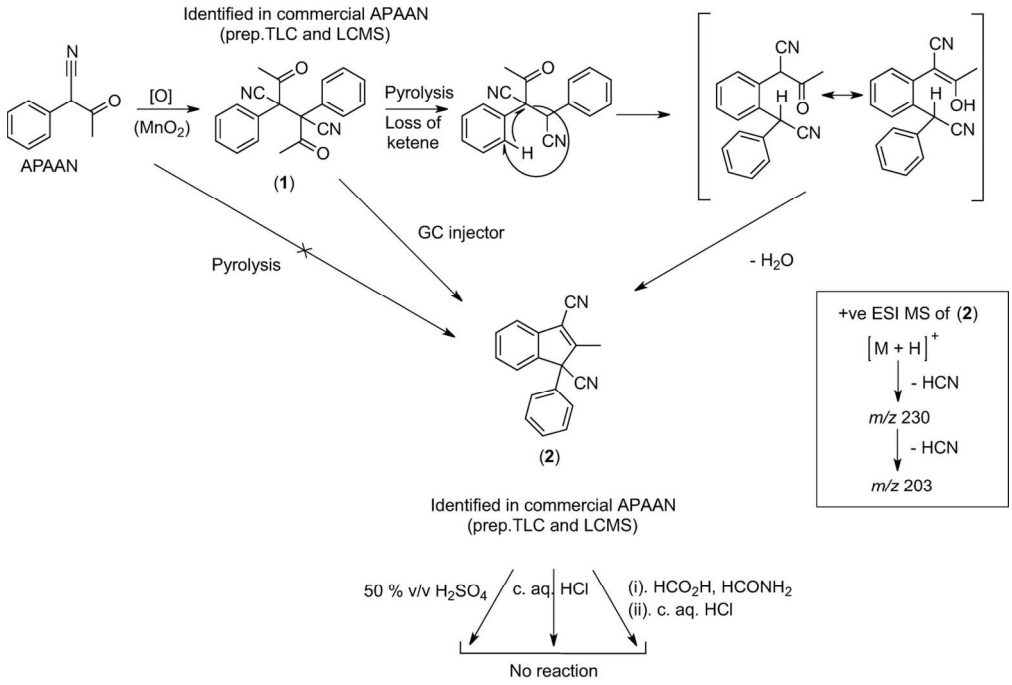

Figure 1. Compounds (**1**) and (**2**) and proposed formation mechanism of (**2**) during pyrolysis of (**1**).
132x89mm (300 x 300 DPI)

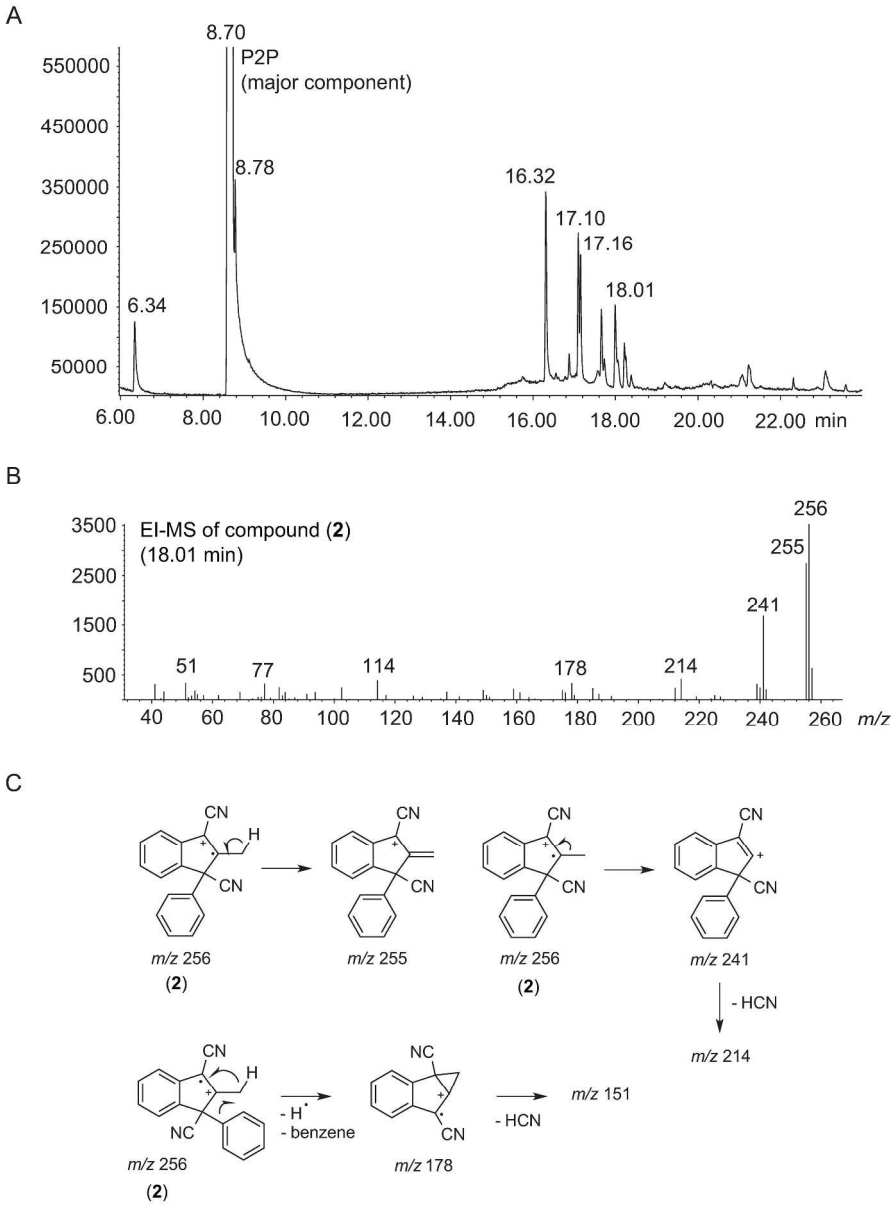

Figure 2. A: GCMS trace of a representative APAAN hydrolysis to P2P (GC-MS method 1). B: Electron ionization mass spectrum of compound (**2**). C: Proposed fragmentation pattern of compound (**2**). 249x337mm (300 x 300 DPI)

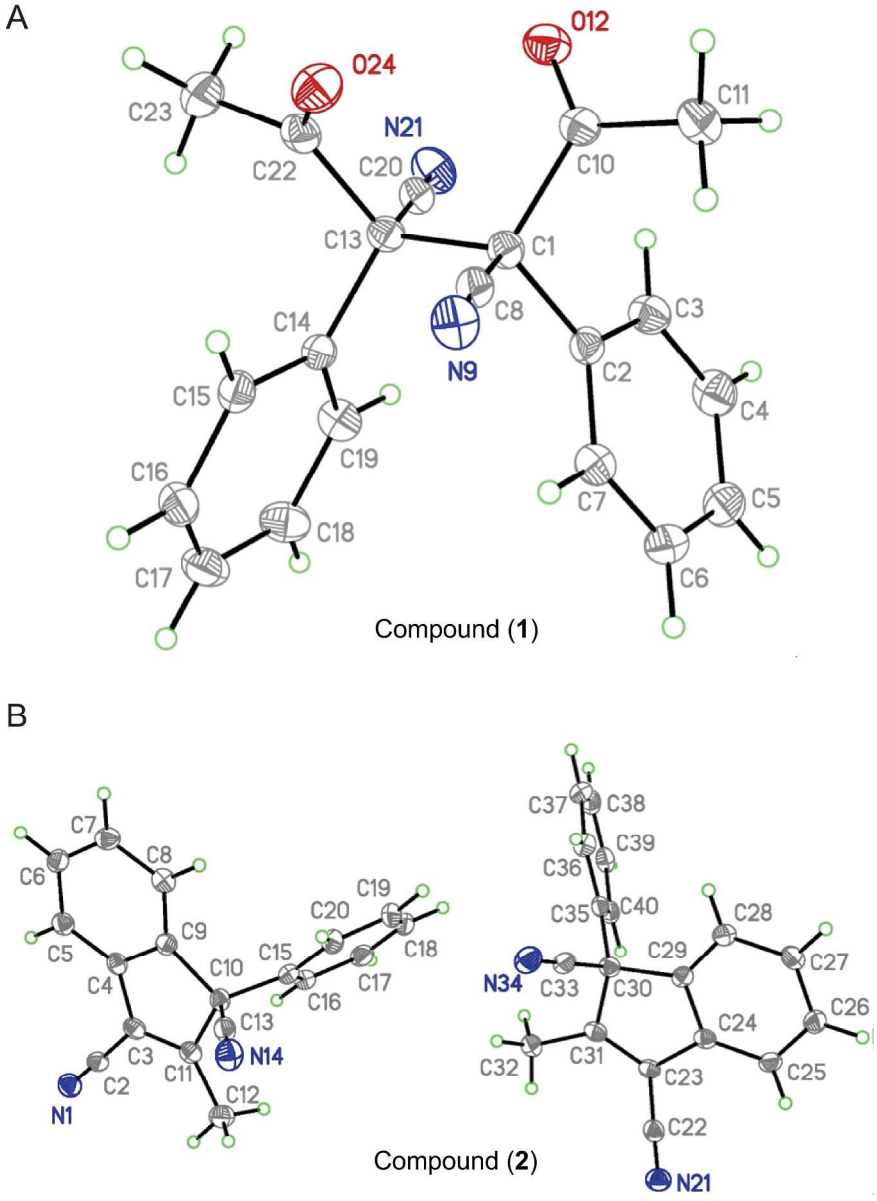

Figure 3. X-ray structures for (**1**) and (**2**).
231x319mm (300 x 300 DPI)

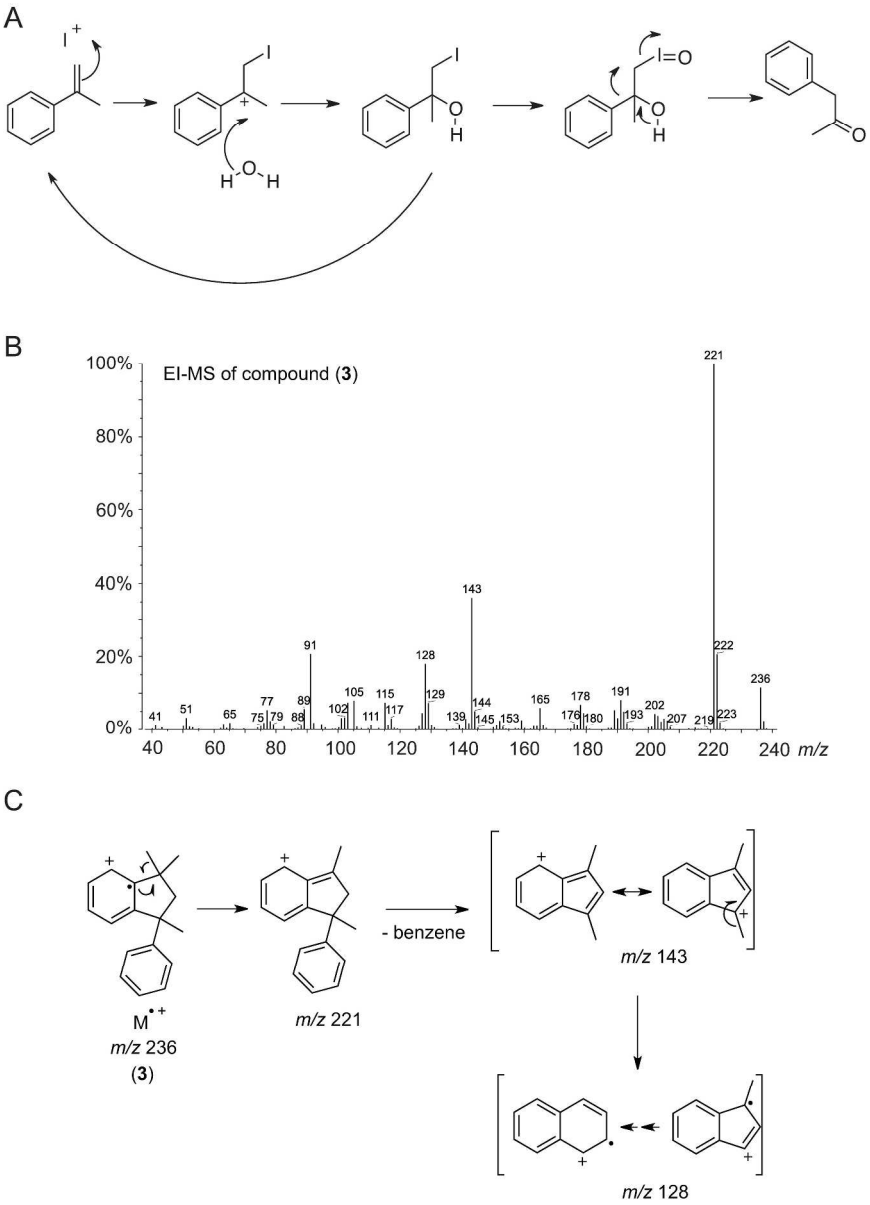

Figure 4. A: 1,2-phenyl shift to yield P2P via an iodosyl intermediate. B: Electron ionization mass spectrum of (**3**). C: Proposed fragmentation pattern of compound (**3**).
269x374mm (300 x 300 DPI)

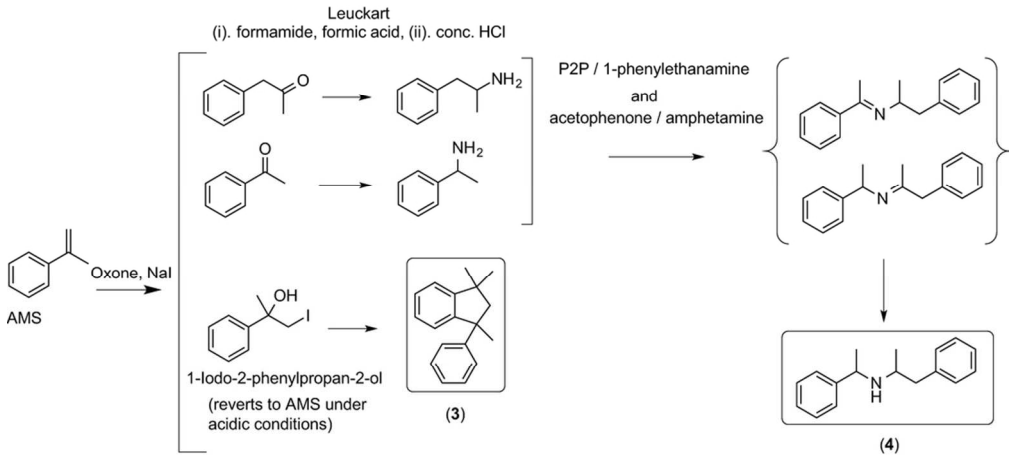

Figure 5. Proposed mechanism of formation of compound (**4**) during Leuckart reaction.
92x41mm (300 x 300 DPI)

Forensic analysis of P2P derived amphetamine synthesis impurities: identification and characterization of indene by-products.

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Abstract

1-Phenyl-2-propanone (P2P) is an internationally monitored precursor that has become increasingly difficult for illicit amphetamine producers to source, which means that alternative routes to its preparation become increasingly important. One such approach includes the hydrolysis of *alpha*-phenylacetoacetonitrile (APAAN) with sulfuric acid. Previously, we reported the identification of 4,6-dimethyl-3,5-diphenylpryid-2-one following implementation of hydrolysis conditions and it was proposed that this compound might serve as one route specific by-product in the APAAN to P2P conversion. This study continued to explore the presence of impurities formed during this conversion and expanded also into a second route of P2P synthesis starting from *alpha*-methylstyrene (AMS). All P2P products underwent the Leuckart procedure to probe the presence of P2P-related impurities that might have carried through to the final product. Two by-products associated with the APAAN hydrolysis route to P2P were identified as 2,3-diacetyl-2,3-diphenylsuccinonitrile (**1**) and 2-methyl-1-phenyl-1,3-dicarbonitrile-1*H*-indene (**2**), respectively. Two by-products associated with the AMS route to P2P and subsequent Leuckart reaction were 1,1,3-trimethyl-3-phenyl-2,3-dihydro-1*H*-indene (**3**) and 1-phenyl-*N*-(phenylethyl)propan-2-amine (**4**), respectively. The two indenes (**2** and **3**) identified in synthesized amphetamine originating from P2P suggested that it might be possible to differentiate between the two synthetic routes regarding the use of APAAN and AMS. Furthermore, the association of these compounds with amphetamine production appears to have been reported for the first time. The presence of compounds **1** – **4** in seized amphetamine samples and waste products could facilitate the suggestion whether APAAN or AMS were employed in the synthesis route to the P2P.

Keywords: APAAN, *alpha*-methylstyrene, P2P, impurities, cyclic indene

Running title: Formation of indene derivatives during synthesis of P2P and amphetamine

Introduction

1-Phenyl-2-propanone (P2P, benzylmethylketone, BMK) is a known precursor used in assorted amphetamine related synthesis routes.[1,2] The Leuckart synthesis route utilizing P2P as the starting material is widely employed by illicit amphetamine and methamphetamine producers in Europe, and increasingly so in America.[3] There are many known synthesis routes to P2P and the most frequently encountered methods are those starting from phenylacetic acid, benzyl cyanide and benzaldehyde, respectively.[4] Commercial trade in P2P is internationally monitored by law enforcement authorities. As the traditional precursors to amphetamine-type illicit substances are under increased scrutiny, it is common for illicit producers to turn to alternative substances as starting materials. *alpha*-Phenylacetoacetonitrile (APAAN), is an example of one such alternative starting material for illicit amphetamine manufacture.[5] APAAN can easily be converted to the more desirable starting material P2P and this may also occur at an amphetamine production site. Increasingly, dedicated 'APAAN to P2P' production sites are increasingly encountered in non-adjoining premises in an attempt to segregate the different synthesis stages in clandestine manufacture and to hinder investigations by law enforcement agencies.[6]

The scale of the use of APAAN in illicit amphetamine can be estimated by an examination of shipment and seizure data. Shipments of APAAN seized in European countries included Poland (800 kg seized in 2010–11), Bulgaria (940 kg seized in 2012), Germany (500 kg in 2012), Hungary (3,000 kg in 2012) and Belgium (23 individual APAAN seizures in 2012). In addition, many clandestine facilities, found to employ the APAAN to P2P conversion have been dismantled in across Europe.[7] Conversely, the confiscated amounts of P2P have decreased dramatically throughout Europe from approximately 5,000 L in 2010 to just 32 L in 2013. APAAN was placed under control in the European Union at the end of 2013. In March 2014, the Commission on Narcotic Drugs of the United Nations voted unanimously in favor of placing APAAN under international control.[7] In 2013, more than 48,000 kg of APAAN was seized using varying types of legislation. [5] The Commission on Narcotic Drugs noted that legitimate uses for APAAN are very limited, and therefore any large imports to Europe were likely to be intended for conversion to P2P. One liter of APAAN yields an estimated 0.7 L of P2P and noting the actual seizures of APAAN in Europe, a concern is that vast quantities of amphetamine or methamphetamine could have been manufactured from APAAN in recent years.[6,7]

The majority of illicit drugs contain impurities that originate from either the synthesis route employed, impurities present in raw materials or from the post-production process.[1] It is essential for the investigation of illicit drug production that information on manufacturing methods, new synthesis routes, the identification of by-products, impurities, new starting materials, contaminants and diluents are collated, reported and made available in the literature for dissemination. There is little information available in the scientific literature about synthetic routes to APAAN or on any by-products that might be formed during its manufacture. Therefore, identification of route-specific impurities would be helpful for investigations linked to cases involving clandestine laboratories.

Previously, our group reported the identification of 4,6-dimethyl-3,5-diphenylpyrid-2-one, an impurity found after acidic hydrolysis of APAAN, which indicated that it might serve as a possible route specific by-product that could remain present in the final amphetamine product.[8] The present investigation extends our research efforts into the identification of impurities that might be formed during acidic hydrolysis of APAAN for amphetamine production. In addition, we also investigated a recently reported method, which utilized arylalkene starting materials, where Oxone® (potassium peroxymonosulfate) and sodium iodide were employed to form the corresponding arylketones in high yield.[9] This method would, in our opinion, seem promising from an illicit P2P manufacturers viewpoint, if *alpha*-methylstyrene (AMS) was used as the starting material. It is readily available and not monitored by authorities and Oxone® is a commercially available pool cleaning agent.

This study reports on the identification of by-products formed during APAAN hydrolysis and the identification and characterization of 2,3-diacetyl-2,3-diphenylsuccinonitrile (**1**) and 2-methyl-1-phenyl-1,3-dicarbonitrile-1*H*-indene (**2**). In addition, 1,1,3-trimethyl-3-phenyl-2,3-dihydro-1*H*-indene (**3**) and 1-phenyl-*N*-(1-phenylethyl)propan-2-amine (**4**) were identified as by-products in the Leuckart reaction of the P2P generated from the AMS synthesis route. The impact on product formation was investigated when changing the concentration of sodium iodide employed in the AMS to P2P procedure.

Experimental

Reagents and standards

All reagents, dry solvents and 1,1,3-trimethyl-3-phenyl-2,3-dihydro-1*H*-indene (**3**) were obtained from Sigma Aldrich Ltd. (Arklow, Ireland). LCMS grade solvents were obtained from Fisher Scientific (Dublin, Ireland).

Syntheses and isolation

Hydrolysis of APAAN with 50 % (v/v) aqueous sulfuric acid

A mixture of APAAN (1.0 g, 6.3 mmol) and aqueous sulfuric acid (50 % (v/v), 12 mL) was heated (oil bath at 120 °C), with constant stirring, for 4 h. The mixture was allowed to cool to room temperature and dichloromethane was added. The organic layer was collected, washed with aqueous sodium hydroxide (2 M), dried (anhydrous magnesium sulfate) and removed to afford a brown oil (460 mg) that represented the crude hydrolysis product of APAAN including P2P and by-products.

*General procedure for the isolation of compounds (**1**) and (**2**) from APAAN, P2P and amphetamine by preparative TLC*

Samples (200 mg) were fractionated by preparative silica gel thin layer chromatography (cyclohexane/ethyl acetate, 200/10) to collect bands corresponding to *R*f values of

compounds (**1**) and (**2**). For the analysis of the (**2**) band, the extracts were reconstituted and diluted appropriately with dichloromethane for GCMS analysis. For the analysis of the (**1**) band, the extracts were reconstituted in acetonitrile/water 1/1, containing 0.1 % formic acid for LCMS analysis.

*The effect of concentrated aqueous hydrochloric acid or 50 % (v/v) aqueous sulfuric acid on compounds (**1**) and (**2**).*

A mixture of (**1**) or (**2**) (5 mg) and concentrated aqueous hydrochloric acid (100 µL) or 50 % (v/v) aqueous sulfuric acid was heated at 110 °C for 6 h. The mixture was allowed to cool to room temperature, diluted with water, made basic with aqueous sodium hydroxide (10 M) and extracted into dichloromethane. The product originating from the reaction with (**1**), the organic layer was collected, blown to dryness with nitrogen and the residue was reconstituted in acetonitrile/water (1/1, containing 0.1 % formic acid) for LCMS analysis. The product originating from the reaction with (**2**) was analyzed by GCMS.

Formation of P2P by oxidation of alpha-methylstyrene ('mixture A' and 'mixture B')

Oxone® (30.7 g, 0.1 mol) and sodium iodide (0.005 mol, 0.75 g) were added to a solution of AMS (5.90 g, 0.05 mol), in acetonitrile/water (5/1, 200 mL) and stirred for 8 h at room temperature. The mixture was initially light brown, then colorless and turned brown again after approximately 7 h, diluted with water (500 mL) and extracted with dichloromethane. The organic extract was washed with aqueous sodium thiosulfate solution, dried (anhydrous magnesium sulfate) and the solvent was removed to afford a light yellow oil. The P2P content in the reaction product ('mixture A', 6.22 g) was estimated at 84 % based on a comparison with P2P reference material using three concentration levels. For the preparation of 'mixture B', a ten-fold higher concentration of sodium iodide (7.5 g, 0.05 mol) was used under identical reaction conditions. A yellow oil (10.85 g), was obtained and found to contain 5 % P2P.

*Isolation of (**3**) from P2P and its Leuckart reaction mixture by preparative TLC*

Samples (200 mg) were fractionated by preparative silica gel TLC (hexane) to collect the band corresponding to the R_f value of compound (**3**). The extracts were evaporated and re-constituted in dichloromethane for GCMS analysis.

Leuckart reaction with P2P obtained from different synthetic routes

A mixture of the corresponding P2P product (1.0 g), formamide (1.0 g, 0.022 mol) and formic acid (1.0 g, 0.022 mol) was heated (oil bath at 150 °C) for 4 h. The mixture was allowed to cool to room temperature. Concentrated aqueous hydrochloric acid (10 mL) was added and the mixture was heated (oil bath 110 °C) for 2 h. The mixture was allowed to cool to room temperature, diluted with water and made basic with aqueous sodium hydroxide (10 M) and extracted with dichloromethane. The organic layer was pooled, dried (anhydrous magnesium sulfate) and the solvent was removed. The P2P products were prepared from the procedures described above: a) 'mixture A' (AMS

oxidation, 563 mg of a brown oil); b) commercially available P2P (718 mg of a brown oil); c) APAAN hydrolysis (770 mg of a brown oil); 'mixture B' (AMS oxidation with increased NaI; 965 mg of a brown oil).

*Exposure of compound (**2**) to Leuckart reaction conditions*

A mixture of compound (**2**) (10 mg), formamide (150 µL) and formic acid (150 µL was heated (oil bath at 120 °C) for 4 h. Concentrated aqueous hydrochloric acid (500 µL) was then added and heating was continued for 2 h. The mixture was allowed to cool to room temperature, diluted with water, made basic (sodium hydroxide) and extracted into dichloromethane. Drying (anhydrous magnesium sulfate) followed by removal of solvent yielded a yellow oil, which was analyzed by GCMS.

*Syntheses of compounds (**1**), (**2**) and (**4**)*

Synthesis methods used for compounds (**1**), (**2**) and (**4**) and 1-iodo-2-phenylpropan-2-ol are summarized as supplemental data 1. Compound **3** was commercially available.

Instrumental analysis

Gas chromatography - mass spectrometry (method 1)

Samples were analyzed on an Agilent 6890N gas chromatograph coupled to a 5973 MSD. A HP-5MS column (30 m × 0.25 mm × 0.25 µm) was used in split-less mode with helium carrier gas at a constant flow of 1 mL/min. The injection port and transfer line temperatures were set at 250 °C and 280 °C respectively. The initial oven temperature was 40 °C, held for 1 min, then ramped at 12 °C/min to 280 °C and held for 5 min, followed by a ramp of 20 °C/min to 300 °C with a final hold time of 3 min. The mass spectra data was collected after a solvent delay of 5 min. The ionization energy was set at 70 eV and the mass range was *m/z* 40-800.

Liquid chromatography - mass spectrometry

LCMS analyses, equipped with an electrospray ionization source, were performed on an Agilent 1100 LC system. The column (Allure PFP Propyl, 5 µm, 50 × 2.1 mm) was from Restek (Bellefonte, PA, USA) and the aqueous mobile phase A consisted of 0.05% formic acid in water whereas mobile phase B was prepared from 0.05% formic acid in acetonitrile, respectively. The Agilent LCMSD settings were as follows: positive electrospray mode, capillary voltage 3000 V, drying gas (N_2) 12 L/min at 350 °C, nebulizer gas(N_2) pressure 60 psi, *m/z* 50-500, fragmentor voltage 180 V. Samples for LC- MS analysis (2 µL injection volume) were dissolved in acetonitrile/water (1:1, containing 0.1% formic acid) at a concentration of 5 µg/mL. The following gradient elution program was used: 0-5 min 12% A and then increased to 35% over 30 min using a linear gradient. The flow rate was 1 mL/min and the column temperature was 30°C.

Nuclear magnetic resonance spectroscopy

Samples were prepared in DMSO-d_6 ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR spectra were recorded on a Bruker AV600 NMR spectrometer using a 5 mm TCI cryoprobe. ^{1}H NMR spectra were referenced to an external TMS reference at δ = 0 ppm.

High-resolution electrospray mass spectrometry

HR-ESI mass spectra were recorded by direct injection into a LTQ Orbitrap Discovery (Thermo Fisher, UK). Samples were dissolved in acetonitrile/water (1:1, containing 0.1 % formic acid) and infused at a rate of 5 µL/min. Full accurate high-resolution (30000) mass scans were performed in positive electrospray mode. Measured accurate masses were within ± 5ppm of the theoretical masses. The following conditions were used: drying gas (N2) 10000 mL/min, capillary temperature 310 °C, spray voltage 4 V, capillary voltage 22 V and tube lens 77 V.

X-ray crystallography

A crystal was mounted on a MiTeGen micromount and data collected using a Bruker APEX Duo CCD diffractometer equipped with an Oxford Cobra cryosystem. Data were collected using ω and ϕ scans, corrected for Lorentz and polarization effects, and integrated using the Bruker APEX program suite.[10] Structures were solved by direct methods and refined with least squares procedures.[11] All non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed geometrically in the calculated positions using a riding model.

Compound (**1**)**:** colorless plate, 0.040 x 0.100 x 0.270mm, T = 100(2)K, $C_{20}H_{16}N_2O_2$, M = 316.35, Mokα radiation (0.71073Å), monoclinic, P21/c, a = 9.0836(4), b = 16.5254(7), c = 11.0183(5)Å, β = 98.8792(18)°, V = 1634.14(12)Å^3, Z = 4, ρ = 1.286 mg/m^3, µ = 0.084 mm^{-1} reflections collected 46288, (θ_{max} = 26.40°, 0.80 Å resolution), independent reflections 3353, $R_{(int)}$ = 0.0990, S = 1.036, R1 = 0.0475, wR2 = 0.1018.*

Compound (**2**)**:** colorless needle, 0.080 x 0.110 x 0.200mm, T = 100(2)K, $C_{18}H_{12}N_2$, M = 256.30, Mokα radiation (0.71073Å), orthorhombic, P212121, a = 8.7061(3), b= 11.6316(4), c = 26.4065(9)Å, V = 2674.08(16) Å^3, Z = 8, ρ = 1.273mg/m^3, µ = 0.076 mm^{-1}, reflections collected = 81867, (θ_{max} = 26.54°, 0.80 Å resolution), independent reflections 5536, $R_{(int)}$ = 0.0584, S = 1.048, R1 = 0.0359, wR2 = 0.0785. (* $R1=\Sigma||Fo|-|Fc|| / \Sigma |Fo|$ and $wR2 = \Sigma w(|Fo|^2-|Fc|^2)^2/ \Sigma w|Fo|^2)^{1/2}$).

Cambridge Crystallographic Data Centre deposition numbers 1407791 and 1407792 contain the crystallographic data reported in this study.[12]

Results and discussion

In this study, impurities associated with samples derived from the hydrolysis of APAAN to P2P followed by the Leuckart reaction were investigated and questions arose about the presence of by-products carried through to the final amphetamine product. Indeed, along with previously reported Leuckart synthesis by-products (most notably naphthalenes, *di*-phenylisopropylamines and formyl-amphetamines) another by-product 4,6-dimethyl-3,5-diphenylpyridin-2-one was recently detected in the APAAN to P2P hydrolysis.[8]

The commercially supplied reagent APAAN utilized in the experiments was stated to be greater than 98% in purity although the synthesis method was not specified. It was noticeable that the commercial APAAN sample also contained darker crystals amongst the off-white material. Analysis by LCMS revealed the presence of the expected APAAN peak but also the appearance of two compounds (**1**) and (**2**) with protonated molecules at *m/z* 317 and *m/z* 257, respectively. Interestingly, an analysis by GCMS, however, did not reveal a chromatographic peak corresponding to a molecular ion at *m/z* 316 (**1**). Only two peaks related to APAAN and (**2**) were observed which suggested that (**1**) was unstable under GCMS conditions.

In each of the subsequent acidic hydrolysis (HCl and H_2SO_4) experiments conducted with APAAN, compound (**1**) was detected in the GCMS chromatograms. Analysis of synthesized (**1**) by GCMS revealed that it was fully converted to a mixture of APAAN and (**2**). The two compounds (**1**) and (**2**) were identified by chromatographic comparison as 2,3-diacetyl-2,3-diphenylsuccinonitrile, a symmetrical dimer of APAAN, and 2-methyl-1-phenyl-1,3 dicarbonitrile-1*H*-indene, respectively (supplemental data 2).

Exposure of (**1**) to the GC analysis led to pyrolysis and it is proposed that this conversion might involve a structural rearrangement *via* initial loss of a neutral ketene and subsequent loss of H_2O to yield (**2**) (Figure 1). The heat of the injection port was sufficient to fully convert (**1**) to (**2**). Compound (**2**) was also confirmed as the pyrolysis product of in-house synthesised (**1**) in separate experiments using a heat gun at a much higher temperatures (supplemental data 3). When APAAN was subjected to similar pyrolysis experiments using the heat gun (to ensure a higher temperature than just that of the GCMS analytical method) it did not form compound (**2**) which confirmed that (**1**) had to be formed first and it alone led to the formation of (**2**).

Structurally, APAAN can be regarded as *alpha*-substituted benzyl cyanide and oxidative *homo*-coupling results in the formation of a new carbon - carbon bond between the two carbons alpha to the carbonitrile functional groups, i.e. resulting in the formation of (**1**). This APAAN dimerization resulted in the formation of both *dl* and *meso* isomers of (**1**) because these type of transformations generally undergo non-diasteroselective radical dimerization processes.[13] Utilizing the differences in solubility of the isomeric forms in the preparative TLC work up, the *dl* isomer was preferentially isolated. The ^{1}H NMR and ^{13}C NMR data further confirmed identification of (**1**) and (**2**). Interestingly, the ^{1}H NMR of (**1**), if isomerically pure for either *dl* and *meso* isomers, would only have one signal for both methyl groups present but two methyl signals in the ratio of 90:10 were observed for (**1**) which reflected the greater abundance of the *dl* isomer of (**1**) following implementation of preparative TLC (supplemental data 4). In the synthesis of the

structurally similar 2,3-diphenyl-succinonitrile, a mixture of *meso* and *dl* isomers is also reported and the synthesis method was altered to favor production of the *meso* isomer.[14] The high resolution electrospray mass spectrometry data for (**1**) gave an accurate mass of 317.1281 consistent with $C_{20}H_{17}N_2O_2$ at *m/z* 317.1285. LCMS data of (**1**) in the presence of the APAAN acidic hydrolysis products is shown in supplemental data 2. Also included are in-source collision induced dissociation spectra at fragmentor voltages of 50 V and 130 V, provided suitable formation of product ions and the presence of $[M + H]^+$ and $[M + Na]^+$ species.

The GCMS chromatogram of a typical APAAN acidic hydrolysis experiment is presented in Figure 2A. The mass spectrum of (**2**) at retention time of 18.01 min showed a base peak at *m/z* 256, a large peak at *m/z* 255 (loss of hydrogen from *m/z* 256), *m/z* 241 (loss of CH_3 from *m/z* 256), *m/z* 214 (loss of HCN from *m/z* 241), 178 (loss of phenyl group and a hydrogen from *m/z* 256 and subsequent rearrangement) and *m/z* 151 (loss of HCN from *m/z* 178) (Figures 2B and 2C).

LCMS electrospray in-source collision induced dissociation experiments with (**2**) at increasing fragmentor voltages (50, 110, 130 and 150 V) yielded ions at *m/z* 230 and *m/z* 203 that resulted from two successive loss of HCN from $[M + H]^+$. In addition to the protonated molecule, the sodiated adduct was also detected The solid-state crystal structures for (**1**) and (**2**) were obtained by x-ray crystallography and confirmed the assignments made (Figure 3, supplemental data 6).

Compound (**2**) contains two nitrile groups and the proposed mechanism of formation of (**2**) from (**1**) by pyrolysis is difficult to envisage by any other mechanism. Compound (**2**) was also unaffected when subjected to acid hydrolysis with various acids, which indicated that its presence might have been carried through to the final amphetamine product stage including utlilization of the Leuckart reaction conditions. The resistance of nitrile groups to acidic hydrolysis in substituted dicarbonitrile heterocyclics has been previously reported.[15] In the case of compound (**2**) the stability of the carbonitriles may have been reinforced due to steric hindrance of the attached phenyl and acetyl groups.

Compound (**1**) was not detected in the Leuckart syntheses of amphetamine employed in-house using P2P (generated *via* APAAN hydrolysis) although compound (**2**) was detected (supplemental data 5). For this reason, compound (**2**) is therefore proposed as a potential route specific marker to the use of APAAN in amphetamine manufacture.

In illicit manufacturing situations, it might be anticipated that the generation of oxidation by-products might become important given the nature of the equipment employed (often not specifically designed for chemical processing) and the often less than ideal reagent sourcing and storage facilities at illicit production sites. In other words, the potential oxidation of APAAN encountered during clandestine situations would predict the trace presence of (**1**) as an impurity in APAAN utilized as the starting material. In the resulting illicit amphetamine products and also in waste products there is the potential to observe both (**1**) and (**2**) in much greater amounts due to the synthesis and processing conditions employed at illicit production sites. Consequently, the finding of such compounds and their analytical data will be of interest to those involved in investigations of clandestine manufacturing facilities.

alpha-Methylstyrene (AMS) synthesis to P2P and its by-products

As previously stated there are many published synthetic routes to P2P.[6] The methods most favored by illicit producers utilize common and easily available starting reagents. A recently reported method applied to the synthesis of ketones involved the occurrence of oxidative 1,2-shifts in 1,1-disubstituted alkenes in the presence of Oxone® and a catalytic amount of sodium iodide (NaI).[9,16-18] In the present study, AMS was used as the alkene in the presence of Oxone® and NaI (10 % molar). The progress of the reaction was monitored by GCMS until depletion of the AMS starting material.

Analysis of this reaction product ('mixture A') was found to contain 84 % P2P, presumably involving the catalytic oxidative 1,2-shift of the phenyl group to yield P2P *via* an iodosyl intermediate generated by the reaction of Oxone® with 1-iodo-2-phenylpropan-2-ol (Figure 4A). The high yield of P2P and the relative lack of other impurities could make this synthesis route a potential method for illicit producers. Benzyl acetate, 1-iodo-2-phenylpropan-2-ol, acetophenone and 2-phenylpropanal were identified as minor by-products alongside the major component P2P in 'mixture A'.

When the synthesis conditions were changed to increasing amounts of NaI, a dramatic change in the ratio of substances obtained in the product was observed. AMS in the presence of Oxone® and an equimolar amount of NaI (a ten-fold increase in concentration compared to the conditions used to prepare 'mixture A') yielded 'mixture B' which contained only 5 % P2P. It is suggested that in the presence the increased amount of NaI, Oxone® reacts with the NaI, reducing the amount of available Oxone® and thus considerably reduces the conversion of 1-iodo-2-phenylpropan-2-ol to the iodosyl intermediate for further conversion to P2P. Instead 1-Iodo-2-phenylpropan-2-ol remained as the major component detected in 'mixture B'. This mechanism and the changes in the major component formed depending on NaI concentration has been previously reported.[9]

In 'mixture A', the Baeyer-Villiger oxidation of any synthesised P2P via potassium peroxymonosulfate (Oxone®) would yield benzyl acetate and this is less likely to occur in 'mixture B' due to the competition from an increased amount of NaI. Interestingly, potassium peroxymonosulfate was the then newly discovered oxidant employed by Adolf von Baeyer and Victor Villiger in their research into the transformation of ketones into esters and cyclic ketones into lactones by peracids in 1899.[19] P2P can be made utilizing the Baeyer-Villiger peracetic acid treatment of 2-acetyl-1-phenylprop-1-ene below 30 °C that results in the formation of 2-acetoxy-1-phenylprop-1-ene. Heating this crude reaction mixture with aqueous HCl at 80 °C was reported to yield P2P.[20] 2-Phenylpropanal, another by-product present in 'mixture A', has also been previously reported via an AMS epoxidation and a subsequent Lewis acid rearrangement.[21] The presence of acetophenone observed in catalytic AMS oxidations might have reflected the formation of an AMS intermediate carrying a benzylic radical center which convert to a cyclic peroxide intermediate. Depending on the reaction conditions, this peroxide intermediate may decompose to acetophenone and formaldehyde or to P2P. Catalytic oxidations of AMS have been studied intensely and a number of products have been identified including linear and cyclic dimers of AMS. Unsaturated linear AMS dimers have been found useful in the production of polymers.[22,23]

When the 'mixture A' was subjected to the Leuckart synthesis, the indene derivative 1,1,3-trimethyl-3-phenyl-2,3-dihydro-1*H*-indene (**3**), i.e. a cyclic AMS dimer, was identified as a by-product during amphetamine synthesis. Compound (**3**) was not detected in the AMS starting material. 'Mixture A' and P2P derived from the APAAN synthesis route were examined and impurity (**3**) was not detected in either, which indicated that (**3**) was formed during the Leuckart synthesis of 'mixture A'. Under acidic conditions, AMS has been previously reported to form (**3**).[24] It is therefore suggested, that the 1- iodo-2-phenylpropan-2-ol which remained present as a by-product in 'mixture A', under Leuckart synthesis conditions forms AMS, which, in turn, was converted into (**3**). Furthermore, when isolated 1-iodo-2-phenylpropan-2-ol was subjected to the Leuckart reaction conditions, compound (**3**) was detected which supported the suggestion that the conversion of 1-iodo-2-phenylpropan-2-ol to AMS under acidic conditions might have occurred (supplemental data 7). Compound (**3**) is commercially available compound and the data obtained during identification was consistent with data previously published.[24] The electron ionization mass spectrum of (**3**) and a proposed fragmentation scheme is shown in Figures 4B and 4C. Consequently, this observation led to the suggestion that the presence of (**3**) might be characteristic to the AMS route to amphetamine via the Leuckart reaction**.**

The Leuckart synthesis on 'mixture A' also yielded unsymmetrical dimers, by combining P2P with 1-phenylethanamine or combining acetophenone with amphetamine resulting in formation of 1-phenyl-*N*-(1-phenylethylidene)propan-2-amine and 1-phenyl-*N*-(1-phenylpropan-2-ylidene)ethanamine. Both of these were reduced to the stable unsymmetrical dimer 1-phenyl-*N*-(1-phenylethyl)propan-2- amine (**4**) (Figure 5). The GCMS chromatogram of (**4**) is provided (supplemental data 8). The presence of (**4**), however, is not characteristic of the AMS route to P2P as it has been previously reported as a by-product present in seized samples of amphetamine.[25]

Many illicit producers do not monitor the ratio of reagents carefully and illicit production operators tend to have little knowledge about the synthesis process itself thus leading to variable product quality. The fact that the concentration of the sodium iodide is critical to obtain a high yield of P2P in the Oxone® oxidation of AMS is one obvious disadvantage to this synthesis route for small-scale illicit amphetamine production. In the examination of Irish custom seizures of imported amphetamine to date no indication has emerged that the AMS route has been used.

Conclusion

International control and monitoring of 1-phenyl-2-propanone (P2P), and more recently *alpha*-phenylacetoacetonitrile (APAAN), has forced illicit producers to explore different unmonitored compounds that can be converted into more commonly used starting materials. This study revealed the presence of (**1**) as a by-product of oxidation and APAAN hydrolysis. This study also revealed the presence of indenes (**2**) and (**3**) that were found in amphetamine products prepared in-house from P2P, which originated from two distinct synthetic routes, i.e. *via* APAAN hydrolysis and oxidation of *alpha*-methylstyrene (AMS). The unsymmetrical dimer (**4**) was formed as a by-product in the Leuckart synthesis of P2P generated from AMS. The presence of compounds **1** – **4** in

seized amphetamine samples and waste products could facilitate the suggestion whether APAAN or AMS were employed in the synthesis route to the P2P.

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Captions:

Figure 1. Compounds (**1**) and (**2**) and proposed formation mechanism of (**2**) during pyrolysis of (**1**).

Figure 2. A: GCMS trace of a representative APAAN hydrolysis to P2P (GC-MS method 1). B: Electron ionization mass spectrum of compound (**2**). C: Proposed fragmentation pattern of compound (**2**).

Figure 3. X-ray structures for (**1**) and (**2**).

Figure 4. A: 1,2-phenyl shift to yield P2P via an iodosyl intermediate. B: Electron ionization mass spectrum of (**3**). C: Proposed fragmentation pattern of compound (**3**).

Figure 5. Proposed mechanism of formation of compound (**4**) during Leuckart reaction.

Supplemental data

1. Synthesis methods for (**1**), (**2**), (**4**) and 1-iodo-2-phenylpropan-2-ol.

2. Assorted analytical data for compounds (**1**), (**2**) and APAAN.

3. Analytical data showing that (**1**) and (**2**) were present at trace levels in commercial APAAN and that the pyrolysis product of (**1**) is (**2**).

4. NMR data for (**1**) (majority of *dl* form present) and (**2**).

5. Compound (**2**) is present in both amphetamine and P2P synthesized from APAAN.

6. X-ray CIFs for (**1**) and (**2**).

7. Analytical data for conversion of 1-iodo-2-phenyl-propan-2-ol to AMS.

8. Analytical data for (**4**).