Case Report

An unusual presentation of a customs importation seizure containing amphetamine, possibly synthesized by the APAAN–P2P–Leuckart route

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A R T I C L E   I N F O

Article history:
Received 19 April 2013
Received in revised form 20 September 2013
Accepted 5 October 2013
Available online 14 October 2013

Keywords:
APAAN
Amphetamine
Amphetamine dimers
P2P
Benzyl cyanide
Pyrimidines
Naphthalenes
Formylamphetamine
Synthetic route and route specific impurities in amphetamine synthesis

A B S T R A C T

During the analysis of an Irish customs seizure (14 packages each containing approximately one kilogram of a white wet paste) were analysed for the suspected presence of controlled drugs. The samples were found to contain amphetamine and also characteristic by-products including benzyl cyanide, phenylacetone (P2P), methyl-phenyl-pyrimidines, N-formylamphetamine, naphthalene derivatives and amphetamine dimers. The analytical results corresponded with the impurity profile observed and recently reported for the synthesis of 4-methylamphetamine from 4-methylphenylacetoacetoneitrile [1]. The synthesis of amphetamine from alpha-phenylacetoacetoneitrile (APAAN) was performed (via an acid hydrolysis and subsequent Leuckart reaction) and the impurity profile of the product obtained was compared to those observed in the customs seizure. Observations are made regarding the route specificity of these by-products.

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1. Introduction

Amphetamine and its related compounds are controlled substances and there have been many studies looking at the synthetic routes for their manufacture [2–4]. There are numerous synthetic approaches to the synthesis of amphetamine type compounds and the exchange of recipes amongst clandestine chemists is prolific. In Ireland, a typical content of amphetamine in street samples has been reported to be between 1% and 10% [5].

In the Irish Republic, the Forensic Science Laboratory (FSL) receives all samples seized by An Garda Síochána (the Irish National Police Force) and Irish Customs Officers for examination under the Misuse of Drugs legislation. A customs seizure (an importation case) was presented to the FSL and analysis confirmed the presence of amphetamine. The seizure consisted of fourteen packages each containing approximately one kilogram of a white wet paste-like material wrapped in assorted layers of plastic and outer foil packaging (see Fig. 1). In the second from innermost layer of packaging there was a yellow liquid that had apparently seeped from the white paste. Amongst the outer layers of plastic packaging and in the foil packaging there was a mixture of brown granules (coffee) and blue/white granules (detergent). These substances may have been added to disguise the smell of the amphetamine containing paste in an effort to avoid canine detection. The white paste was found to contain amphetamine and a mixture of various compounds, including phenylacetone (P2P), benzyl cyanide (phenylacetoacetoneitrile), pyrimidines, N-formylamphetamine, amphetamine dimers and naphthalene derivatives. The yellow liquid was found to contain greater concentrations of these by-products. The analytical results for the yellow liquid and the white paste corresponded with a by-product profile recently observed and reported for the Leuckart synthesis of 4-methylamphetamine from 4-methylphenylacetoacetoneitrile [1]. Consequently, it was proposed that the amphetamine in...
this importation case might have been synthesized from by hydrolysis of alpha-phenylacetacetointrile (APAAN) to P2P followed by a Leuckart reaction.

In Europe, the major synthetic route for most amphetamine syntheses is the Leuckart reaction of phenylacetone (P2P, BMK, benzyl methyl ketone, phenylacetone) [6–8]. In this route, condensation of formamide with P2P at elevated temperatures results in the formation of an intermediate N-formylamphetamine and its subsequent hydrolysis yields amphetamine and also numerous by-products. Many investigations have sought to identify route specific impurities for the distinct synthetic routes to amphetamine or substituted amphetamine production, i.e. unique by-products [9–17,18–21]. To circumvent international control measures, P2P has been made from various ‘pre-precursors’, most typically from APAAN, which may be synthesized from benzyl cyanide, benzaldehyde, or phenylacetic acid, [10]. Recent reports have highlighted the increase in the seizures of APAAN in Europe and also that some European criminal groups have imported and/or synthesized APAAN [8,11]. APAAN is not currently listed as a controlled substance under international precursor regulations or as a controlled drug under Irish national legislation.

To investigate the proposal that the amphetamine in this importation seizure may have been produced from APAAN, a laboratory synthesis was performed and the by-product profile of the resulting amphetamine was found to be very similar to that of the customs sample.

2. Materials and methods

2.1. Reagents and standards

All reagents and dry solvents used in the syntheses were obtained from Sigma Aldrich Ltd. (Arklow, Ireland).

2.2. Synthesis of P2P from APAAN and its further conversion to amphetamine

2.2.1. APAAN to P2P

APAAN, alpha-phenylacetacetointrile (5 g) was added to water (30 ml) and concentrated sulfuric acid (30 ml) was added drop-wise, keeping the temperature below 10 °C. The mixture was then heated (oil bath, 150 °C) with vigorous stirring for 4 h and allowed to cool to room temperature. This was then partitioned between dichloromethane and water, the organic layer collected, washed with saturated aqueous sodium bicarbonate, dried (anhydrous magnesium sulfate) and evaporated to dryness to give a light brown oil (3.2 g).

2.2.2. Amphetamine, Leuckart synthesis

A portion of the oil (0.75 g), formamide (240 mg) and formic acid (140 mg) was heated at 150 °C for 4 h. The mixture was allowed to cool to room temperature, concentrated hydrochloric acid (4 ml) was added and the mixture was refluxed for 2 h. This was then allowed to cool to room temperature, diluted with water, made basic (sodium hydroxide), extracted with dichloromethane, the organic layer collected, dried (anhydrous magnesium sulfate) and evaporated under water aspirator vacuum at 30 °C to give a brown oil (770 mg).

2.3. Sample analysis

2.3.1. GCMS

Samples were prepared by dissolving approximately 1 mg of each in 1 ml methanol and analysed on an Agilent 6890N GC coupled to 5975 Mass Selective Detector. A HP-ULTRA 1 column (12 m x 0.2 mm x 0.33 μm) was used with helium carrier gas at a constant flow of 1 ml/min and a split ratio of 50:1. The injector was set at 250 °C and the transfer line at 280 °C. The initial oven temperature was 60 °C, held for 2 min then ramped at 25 °C/min to 295 °C with a hold time of 3 min. The mass spectra were collected after a 1.5 min solvent delay time. The ionization energy was set at 70 eV and the mass range was m/z 40–450.

3. Results and discussion

In the examination of the fourteen packages seized by Irish Customs, it was noted that no typical adulterants or diluents were found to be present; this suggests that the seized material came directly from the illicit production site or that no post synthesis adulteration of the product had taking place prior to the attempted importation into Ireland. The white paste and the yellow liquid from the customs importation seizure were each found to contain amphetamine and a mixture of various compounds, including P2P, benzyl cyanide, 4-methyl-5-phenylpyrimidine, 4-benzylpyrimidine, N-acetylamphetamine, N-formylamphetamine, di-[(β-phenylisopropyl)amine isomers, 1-benzyl-3-methylnaphthalene and 1,3-dimethyl-2-phenyl-naphthalene. The white paste was similar in profile to the components found in the yellow liquid but the byproducts were less abundant (see Fig. 2a and b). The yellow liquid was found to contain 8% amphetamine (calculated as freebase) while the wet white paste was found to contain 24% amphetamine (calculated as freebase). Some of the paste was allowed to air dry.

Fig. 1. Montage of photographs of a package containing amphetamine.
and the resulting powder (which now had a slight yellow colour) was found to contain 60% amphetamine (calculated as freebase). The counter ion was identified as sulfate.

The samples from this seizure contained by-products (pyrimidines, dimers and naphthalenes) which were previously reported and thought to be route specific for two different synthesis routes to the production of amphetamine and methamphetamine, namely the Leuckart reaction of P2P to yield amphetamine (or methamphetamine) and the Nagai synthesis, a non-metal reduction of ephedrine using hydroiodic acid/red phosphorus to produce methamphetamine [6–8].

It has been reported that 1-benzyl-3-methylnaphthalene and 1,3-dimethyl-2-phenyl-naphthalene are considered route specific for the ephedrine/hydroiodic acid/red phosphorus route to methamphetamine. It is known that a by-product of the Nagai synthesis of methamphetamine from ephedrine is 1,2 dimethyl-3-phenylaziridine, which may undergo hydrolysis to yield P2P. This P2P could react with strong acids to yield naphthalenes [14,16]. 4-Methyl-5-phenylpyrimidine, 4 benzylpyrimidine and di-(β-phenylisopropyl)amine have all been considered route specific for amphetamine synthesis via the Leuckart reaction [6,16,20,21]. Doubt has been cast on the route specific nature of the 4-methyl-5-phenylpyrimidine and 4-benzylpyrimidine for the Leuckart synthesis, these compounds have also been detected in reductive amination routes [9]. The presence of the di-(β-phenylisopropyl)amine isomers (dimers) have been linked to the Leuckart synthesis of amphetamine type compounds [17,20,21].

Our laboratory Leuckart synthesis starting with P2P, made from APAAN, yielded amphetamine that had the same characteristic component by-products present as in the customs importation seizure. The presence of naphthalenes suggests that P2P was exposed to a strong acid, one plausible explanation is that they were produced by the acidic hydrolysis of APAAN. The relative abundances of the by-products were different which is unsurprising as it has previously been reported that the exact conditions of the synthesis can greatly affect yields [7,17]. The conversion of APAAN to P2P (see Fig. 2c) clearly shows the presence of 1-benzyl-3-methylnaphthalene and 1,3-dimethyl-2-phenyl-naphthalene. In the APAAN synthesis to P2P, it was the crude product (i.e. without any distillation of the P2P) that was used in the Leuckart Amphetamine synthesis. This reaction yielded amphetamine and also 4-methyl-5-phenylpyrimidine, 4-benzylpyrimidine, N-formyl-naphthalene and di-(β-phenylisopropyl)amine dimers (see Fig. 2d). If distillation of the P2P made from the APAAN had been performed a considerably purer P2P would have resulted (the naphthalenes are relatively non-volatile), thus leading to the potential absence of naphthalenes found in the final Leuckart amphetamine product. This suggests that a “crude” P2P was used in the synthesis of the amphetamine in the customs seizure and it may indicate that the illicit producers simplified the clandestine manufacturing process by removal of the distillation step.

The synthesis route from APAAN via acid hydrolysis to P2P and its subsequent Leuckart reaction to yield amphetamine has shown that both naphthalenes and expected Leuckart by-products are obtained. Thus, the detection of naphthalenes in amphetamine may no longer be considered route specific to an ephedrine based route.

In a subsequent acidic extraction of the customs seizure the presence of benzyl cyanide was noted (chromatogram not shown). This was a surprising find in a number of respects. The acid hydrolysis of APAAN in our laboratory yielded P2P and the two naphthalenes, along with other by-products, but no APAAN or benzyl cyanide remained. It would be expected that benzyl cyanide would be hydrolysed to phenylacetic acid in the presence of a strong acid. It is possible that the APAAN used in the illicit manufacture of the amphetamine was grossly contaminated with
benzyl cyanide which was not fully hydrolysed. It is also possible that the P2P may have been contaminated with benzyl cyanide following the hydrolysis.

4. Conclusion

A customs importation case was found to contain amphetamine. Some of the impurities found along with the amphetamine were previously reported to be route specific for both amphetamine synthesized via the Leuckart synthesis route utilizing P2P and also for methamphetamine synthesized via the Nagai synthesis utilizing ephedrine. Both P2P and ephedrine are known precursors to many amphetamine type stimulants and both are under international control. It has been demonstrated that the acid hydrolysis of APAAN yields naphthalenes. The Leuckart conversion of P2P from the APAAN to amphetamine yields the majority of the other components found in the importation seizure. This APAAN-P2P-Leuckart impurity profile, and specifically the formation of the naphthalenes, has implications for the determination of the synthetic route from seized samples of amphetamine type stimulants. The presence of naphthalenes in amphetamine seizures is indicative of a process where P2P was exposed to strong acid and one reasonable explanation is the synthesis of P2P by the acidic hydrolysis of APAAN.

Acknowledgements

The authors wish to acknowledge Mr. Eoin Conway for Photographic assistance and all Colleagues at the Forensic Science Laboratory and at the Department of Pharmacology and Therapeutics, Trinity College Dublin, Ireland.

References

[5] Personal communication, Amphetamine purity levels in Ireland.