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Anise oil as para-methoxyamphetamine (PMA) precursor

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Abstract

These days, MDMA is one of the most popular drugs of abuse. Due to its illegality, MDMA and its chemical precursors are watched by governmental organizations in many countries. To avoid conflicts with legal instances, underground chemists have tried to market several new unregulated amphetamine analogues, such as 4-MTA. Para-methoxyamphetamine (PMA), on the other hand, is regulated by law but its precursors are easily obtained since they are cheap and unwatched. This article presents such a case, namely the large scale synthesis of PMA using anethole, a main constituent of anise oil, as precursor. Anethole has been converted to its phenyl acetone analogue via peracid oxidation, while PMA itself has been synthesized using this ketone as precursor in the Leuckart synthesis. The synthesis of PMA using anethole as starting product has been investigated applying GC/MS and GC-HSPME/MS techniques, hereby discovering new specific (4-methoxyphenol) and already identified synthesis impurities (4-methyl-5-(4-methoxyphenyl)pyrimidine, *N*-(β-4-methoxyphenylisopropyl)-4-methoxybenzyl methyl ketimine, 1-(4-methoxyphenyl)-*N*-(2-(4-methoxyphenyl)-1-methylethyl-2-propanamine, 1-(4-methoxyphenyl)-*N*-methyl-*N*-(2-(4-methoxyphenyl)-1-methylethyl-2-propanamine, *N*-(β-4-methoxyphenylisopropyl)-4-methoxybenzaldimine). The new impurity 4-methoxyphenol is specific for the application of a peracid oxidation method where anethole is used as precursor.

Keywords: Anise oil; Anethole; Para-methoxyamphetamine; Leuckart reaction; 4-Methoxyphenol

1. Introduction

For many years, several recreational drugs are available on the clandestine market. Especially phenylethylamine derivatives such as amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA) are very popular. Para-methoxyamphetamine (PMA, 4-MA) is a phenylethylamine derivative as well, but unlike the others previously mentioned, it has a very poor reputation due to its association with several deaths in the past.

PMA should not be confused with 4-MTA, 4-methylthioamphetamine. The latter is a relatively new designer drug that has been encountered on the clandestine drug market in The Netherlands, UK, Australia and Germany in the late 1990s [1–3]. 4-MTA and PMA only differ in their molecular structure by one atom: the oxygen in the para-methoxy group of PMA has been substituted by a sulphur atom. Its production was possibly an attempt to circumvent legal problems.

Until early to mid-2001, there have been no reports on the circulation of PMA on the clandestine Belgian drug market. In July 2001, three people tragically died of a PMA overdose. The police found some beige pills with an 'xTc'-logo pressed on one side. Examination of the pills indicated the presence of PMA. This was the first physical evidence of the circulation of PMA on the Belgian drug market. After the fatal July cases, it remained fairly calm regarding PMA until the Christmas period of 2001, when beige powders have been found.

The illicit synthesis of PMA is poorly described in relation to other amphetamine derivatives as methamphetamine, MDA and MDMA. The ''classic'' pathway uses para-methoxybenzaldehyde as precursor [1,4a,5]. The possibility of using anethole as precursor has recently been briefly mentioned by Blachut et al. in their research of specific Leuckart impurities using para-methoxyphenyl-2-propa-

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none (PMP2P) as precursor [6]. Anethole is the main constituent of anise oil (anise oil from *Pimpinella anisum* contains 80–90% anethole, anise oil obtained from *Illicium verum* 75–90%) [7a,7b]. It can also be found in fennel oil (50–60%). Methyl chavicol (estragole), a constituent of Tarragon oil [7c,7d], is in theory a possible precursor as well (after isomerization to anethole in boiling alcoholic KOH [8]). A. Shulgin used para-methoxybenzaldehyde as precursor for PMA [4a], PMP2P for PMMA [4b] and refers [4c] to the potential usefulness of anethole or methyl chavicol. This paper investigates the possibility to synthesize PMA via the Leuckart reaction (and hence PMMA) using anethole, obtained from essential oils, as precursor.

2. Methods and techniques

2.1. Gas chromatography and mass spectrometry

2.1.1. GC/MS: liquid injections

As gas chromatograph-mass spectrometer (GC/MS), an Agilent 6890 Plus equipped with a 5973N Mass Selective Detector and electronic pressure programming has been used (Agilent, USA). For liquid injections, a standard split/splitless deactivated liner was utilized. The applied column was a HP-5MS (Agilent, USA) capillary column (30.0 m × 0.250 mm × 0.25 μm). The carrier gas was helium, applied at a constant flow rate of 1 ml/min. The oven temperature was programmed as follow: 50 °C for 1 min, 35 °C/min to 100 °C, 10 °C/min to 270 °C. This temperature was maintained until the end of the programmed run (39.43 min). The injection port was run in the split or splitless mode (depending on the nature of the sample) at a temperature of 250 °C. The mass spectrometer (MS) was used in electron impact (range from 35 to 800 amu) with an ionization energy of 70 eV. A solvent delay time of 4 min was applied.

2.1.2. GC/MS: headspace solid-phase microextraction (HSPME)

For HSPME via GC/MS, the same apparatus as described in Section 2.1.1 has been used. Some settings have been changed: the MS was used in electron impact (range from 22 to 500 amu) with an ionization energy of 70 eV; no solvent delay time was applied. The injector port was run in the split or splitless mode at a temperature of 260 °C. A glass liner of 0.75 mm i.d. was used and operated at 260 °C. The oven went from 50 °C (no delay) to 300 °C at a rate of 30 °C/min. This temperature was maintained until the end of the run (20.33 min).

2.2. Materials

The solid-phase microextraction fiber holder was manufactured by Supelco (USA). The fibers were coated with 100 μm polydimethylsiloxane (PDMS, color code red) or 85 μm polyacrylate (PAC, color code white) solid phase, both manufactured by Supelco.

2.3. Sample preparation

2.3.1. Liquid–liquid extraction of PMA samples

Basic extraction: A portion (35–45 mg) of a PMA (or other amphetamine derivatives) preparation was brought in a solution of 5 ml dichloromethane (DCM) and 5 ml 10% sodium bicarbonate. The solution was mixed thoroughly in a rotamix device for ca. 20 min and centrifugated at 3000 rpm for 20 min. The DCM phase was isolated and blown to dryness using nitrogen gas. The concentrate was dissolved in 200 μl isooctane and a 1 μl aliquot was injected into GC/MS.

Acid extraction: Same procedure, with this exception that the sodium bicarbonate has been replaced by a sodium phosphate buffer at pH 6.5.

2.3.2. HSPME of PMA samples

A portion (50–75 mg) of a PMA preparation was placed in a 5 ml vial. The vial was sealed with a teflon-faced black rubber septum and plastic cap. The samples were equilibrated at room temperature for about 1 h. Then, the adsorbent HSPME fiber was exposed to the sample's headspace (the fiber is not allowed to touch the sample's solid or liquid phase) during 5 min at 60 °C. The fiber was then withdrawn into the needle and placed into the GC's injector. When the fiber was exposed to the injector's interior, desorption was allowed for 1 min.

2.3.3. Screening of illicit heroin samples

To determine the presence of heroin in street drug samples (read further), we used a fast GC/MS screening method: a 5 mg street drug sample was brought into a vial containing a solution of 500 μl chloroform and 100 μl pyridine. The solution was shaken thoroughly and allowed to rest for 2 min. One microliter was injected into GC/MS.

To screen for the presence of sugar compounds, 100 μl BSTFA (bis-(trimethylsilyl) trifluoroacetamide) was added to the solution and allowed to react overnight at room temperature. One microliter was injected into GC/MS [9].

2.4. Synthesis

2.4.1. Synthesis of p-anisic acid

4-Methoxybenzaldehyde (6.0 g) was dissolved in 100 ml DCM and intensely stirred. Four millileter H_2O_2 (35%) was added while stirring. DCM was chosen since it is inert towards H_2O_2. The mixture was allowed to reflux at 35 °C for ca. 20 h (stirring necessary). No change in color has been noted. The 100 ml KOH (10%) was added to dissolve the formed *p*-anisic acid in the aqueous layer. It was separated and concentrated HCl was added drop by drop. A white foamy substance appeared on the surface. The foam was separated and dried in the oven to evaporate the moisture, resulting in small white crystals. GC/MS screening

(split injection 50:1) of crystals dissolved in MeOH indicated *p*-anisic acid as main component and 4-methoxybenzaldehyde as only impurity.

2.4.2. Synthesis of 4-methoxyphenol

Twenty-three grams H_2O_2 (30%) was added to 19 ml HCOOH (98–100%) to synthesize performic acid. The latter was added to an intensely stirred solution of 4-methoxybenzaldehyde (12 ml) in 200 ml DCM (DCM was chosen since it is inert towards H_2O_2). The stirred mixture was allowed to reflux at 39 °C for ca. 20 h. The performic acid was added in 5 ml quantities with 15 min intervals. Initially, the reaction mixture was colorless, but after half an hour, a pale yellowish shine appeared. During the reaction, the color became more intense and changed to yellow-brown. When the reaction was finished, the DCM phase was isolated and the solvent removed via vacuum distillation. Then, 200 ml NaOH (20%) and 75 ml MeOH were added. The mixture was stirred for 1 h. MeOH was removed with vacuum distillation and the alkaline mixture was acidified with HCl (32%) till pH 1. The mixture was extracted with 2× 150 ml DCM. The DCM extracts were combined and the solvent was removed via vacuum distillation. The 10.5 g of a brown liquid that easily solidified upon contact with air remained. GC-HSPME/MS analysis indicated 4-methoxyphenol as main component. Purified 4-methoxyphenol was white.

2.4.3. Synthesis of PMP2P

Twenty-four grams H_2O_2 (35%) was added to 35 g HCOOH (98–100%); the mixture was allowed to form performic acid for 30 min, and was then added to a mixture of 17.5 g undistilled anise oil and 150 ml DCM. Addition of the performic acid to the stirred anise oil/DCM mixture occurred as follows: since the reaction mixture temperature wasn't allowed to surpass 40 °C, performic acid was added in 5 ml aliquots if the temperature allowed it, i.e. if the reaction mixture temperature was not higher than 36–37 °C. To accomplish this, the reaction mixture temperature was checked every 5 min. If the temperature was more than 36–37 °C, no performic acid was added; in case of a lower temperature read-out, 5 ml performic acid was added with a pipette. This process was continued till all performic acid was added (120 min). Then, the reaction mixture was refluxed at 39 °C for 21 h. The DCM phase was isolated and the aqueous phase washed with 2× 50 ml DCM. The combined DCM phases were washed with 100 ml NaOH (5%), after which the aqueous phase was washed with 50 ml DCM. The solvent was removed from the combined organic phases via rotavap. This yielded 24.3 g of a dark red/brownish oil. To this oil, 100 ml MeOH and 400 ml H_2SO_4 (15%) were added. The mixture was refluxed for 2 h and the ketone was isolated by extracting the mixture with 3× 75 ml DCM. The combined DCM phases were washed with 100 ml distilled water, followed by a wash with 100 ml NaOH (5%). The solvent was stripped of with a rotavap, yielding 14 g of a dark brown oil with a fruit-like/spicey odour.

2.4.4. Synthesis of PMA via Leuckart

Three gram of undistilled PMP2P synthesized as in Section 2.3.3, was dissolved in a mixture of 10 ml formamide and 5 ml formic acid (98–100%). The mixture was refluxed for 12 h at 165 °C, after which it was allowed to cool down to room temperature. Ten milliliters concentrated HCl (32%) was added and the mixture was set to reflux for 4 h. Then, the reaction mixture was alkalized with 10% KOH and extracted with 3× 25 ml DCM. The pooled organic fractions were stripped from solvent with a rotavap. A dark brown oil remained. The latter was dissolved undistilled in EtOH and dropped in a solution of H_2SO_4 (10%) in EtOH. This yielded a beige precipitate.

3. Results and discussion

3.1. Primordial examination of clandestine PMA powder

Marquis tests on clandestine PMA powders applied by the police yielded positive results for heroin, ''brown sugar''. The brownish powder color consolidated this result. Upon arrival of the powder at the lab, it was screened for the presence of heroin (cf. 2.2.3). GC/MS didn't find any heroin or substances that can be expected to be found in heroin samples (e.g. papaverine), but it reported the presence of PMA. Reanalysis with derivatization did not reveal any trace of heroin and reindicated the presence of PMA. The derivatization procedure had the advantage that we were able to spot the presence of glucose. Glucose could be responsible for the false positive Marquis test performed by the police. On comparison between the PMA powder and some ''brown sugar'' samples, the latter generally appeared darker colored.

The 100 mg of the beige PMA powder was dissolved in 5 ml methanol. The brownish color disappeared within seconds, resulting in bright white crystals. A precipitation test showed that PMA was present as a chloride salt.

3.2. Synthesis

The oxidation of phenylpropenes to phenyl-2-propanones is a classic method in the synthesis of clandestine amphetamines and its derivatives. To produce amphetamine or methamphetamine, methylstyrene can be oxidized to phenyl-2-propanone (P2P, also known as BMK, benzyl methyl ketone) [10]; to synthesize MDA or MDMA, isosafrole can be oxidized to 3,4-methylenedioxyphenyl-2-propanone (MDP2P) [11]. By analogy with the previous examples, the synthesis of PMA and PMMA (para-methoxymethamphetamine) by oxidation of para-methoxyphenyl-1-propene (anethole) to PMP2P can be suggested.

Peracid oxidation (especially performic oxidation) of propenyl to propanone is a very commonly applied proce-

dure. Dal Cason et al. [10] describe a modified Fugisawa–Deguchi method for the synthesis of P2P. The chemical aspects of this method's popularity can be found in the easiness of the synthesis and the use of simple compounds (no 'exotic' catalysts as Pd or Pt). Generally, performic acid (generated by making a mixture of H_2O_2 and HCOOH) is added to a solution of a phenylpropenyl compound in acetone. The phenylpropenyl reacts with performic acid to yield the phenylpropenyl epoxide. This epoxide is converted to a phenylpropenyl formyl glycol by HCOOH. A strong acid (in most cases H_2SO_4) is used to hydrolyze the ester and convert the obtained glycol to its corresponding P2P derivative. A visual comparison is drawn between the peracid oxidation of isosafrole (for the production of MDMA and/or MDA) and anethole (for the synthesis of PMA and/or PMMA) in Fig. 1.

The synthesis of P2P and MDP2P has been described many times before, though the synthesis of PMP2P using the same method has only been assumed by analogy. Consequently, the synthesis of PMP2P from anethole was one of our goals. The application of a two-phase DCM/peracid system resulted in some advantages compared to the classic use of acetone as solvent. One of the drawbacks using acetone is the exothermic reaction that arises by adding the H_2O_2/HCOOH to the acetone/propenylbenzene derivative mixture. The permanent cooling is very important and could render the method impractical. By using DCM as solvent, one can avoid the loss of performic acid and heavy exothermic reactions, though it has the disadvantage that performic acid and DCM are inmiscible. Since anethole dissolves very well in DCM, continuous stirring of the organic and aqueous phase is critical. Using DCM has the added advantage that it is easy to sample the reaction mixture without taking up any acidic compounds that could damage the chromatographic setup.

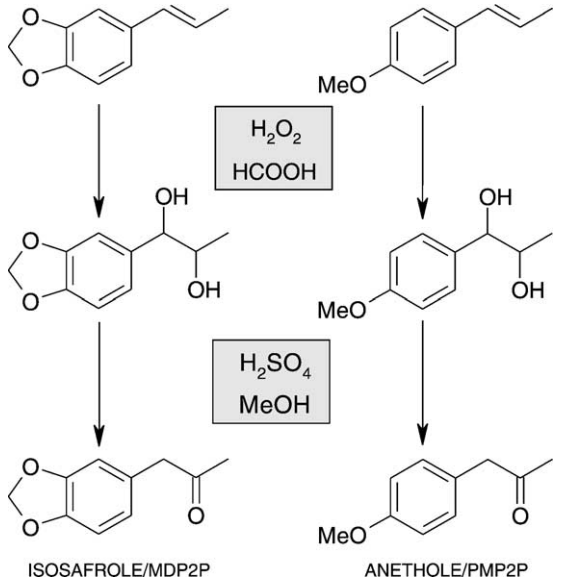

Fig. 1. Analogy between peracid oxidation of isosafrole and anethole.

Fig. 2 is a GC-HSPME/MS (split ratio 50:1) chromatogram of anise oil (harvest year 2000, China). The main peak in this chromatogram (A) consists of anethole, though the other peaks indubitably stand for a variety of volatile components. To increase the yields of the reaction, anise

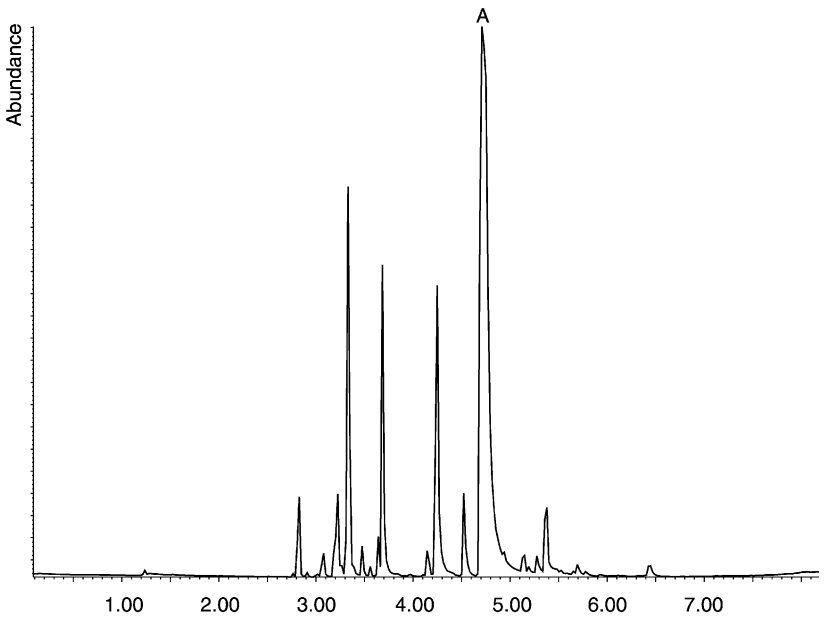

Fig. 2. GC-HSPME/MS chromatogram (split ratio 50:1) of fresh anise oil: A = anethole.

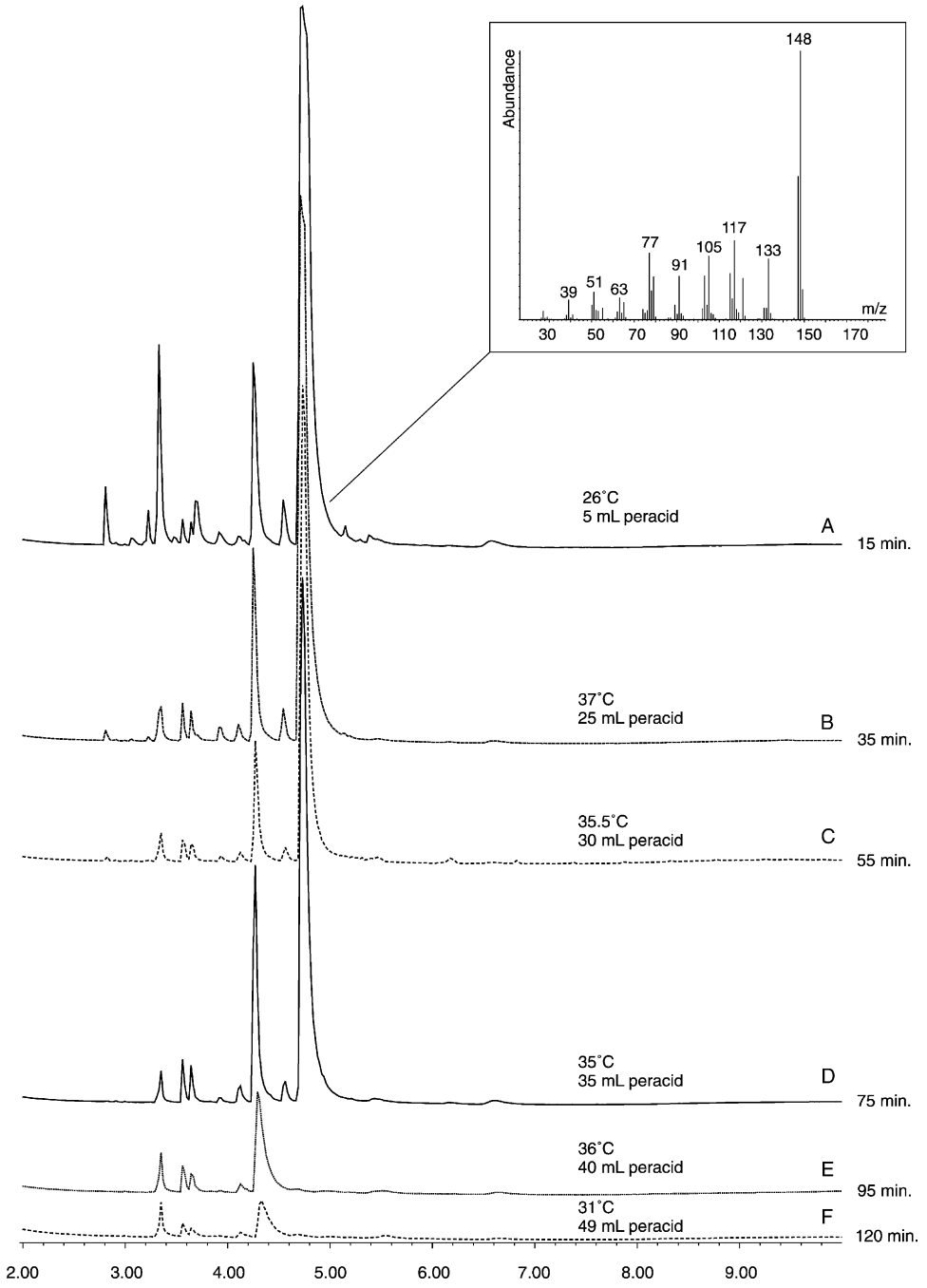

Fig. 3. GC-HSPME/MS chromatograms, split (ratio 50:1). The chromatograms should be interpreted from A to F (following the time dimension). The most abundant peak in chromatogram (A) represents anethole. It is clearly demonstrated that anethole suddenly 'disappears' from the DCM phase. The mass spectrum of anethole is added in chromatogram (A).

oil should be distilled under reduced pressure to obtain pure anethole. By removing the impurities, less side reactions will occur and a more pure end product can be obtained. Since our research is of forensic importance, and is less aimed at developing high yield procedures, we decided not to distill our anise oil and to follow the development of the 'impurities' present in anise oil.

Fig. 3 shows the development of anethole and anise oil impurities during the reaction. The six chromatograms (A to F) display GC-HSPME/MS (split ratio 50:1) chromatograms

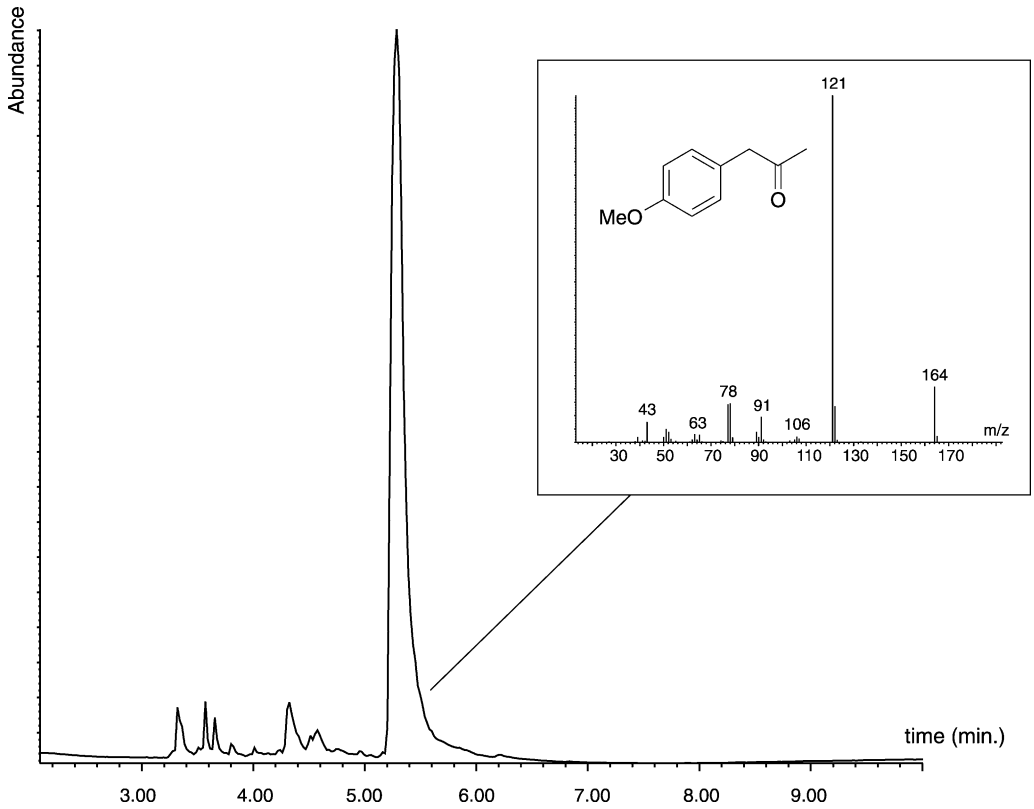

Fig. 4. GC-HSPME/MS chromatogram of undistilled PMP2P oil with PMP2P's mass spectrum.

of samples taken from the DCM phase at different points in time and with different amounts of performic acid added. The samples are taken during the first reaction step in the synthesis of PMP2P from anethole, i.e. the reaction between anethole and the performic acid yielding the glycol (ester). The superposition of the chromatograms demonstrates that some substances disappear while others arise. The rather sudden disappearance of anethole from the DCM phase is remarkable. Using split injection, no more traces of anethole can be found in chromatogram E, while its presence in chromatogram D (sampled 20 min earlier) is obvious. At this point in time, the color has been shifted from colorless to yellowish. During the reaction, traces of PMP2P and the glycol ester are found. At the end of the reaction, the mixture's color has shifted to orange/brown.

A GC-HSPME/MS chromatogram (split ratio 25:1) of the obtained PMP2P (synthesized from the glycol by the pinacol rearrangement) is given in Fig. 4. The chromatogram clearly demonstrates the presence of several impurities. These impurities are probably oxidation products of anise oil components other than anethole. Further purification of PMP2P can be achieved by distillation under reduced pressure. The used method can easily be upscaled and higher yields could be possible, by using for instance phase transfer catalysts (PTCs) and controlling the pH with buffers.

The undistsilled PMP2P was used to synthesize PMA via the Leuckart reaction as described in Section 2.4.4. The resulting PMA oil was screened with GC-HSPME/MS. The main component was PMA, with a trace of PMMA. No other amphetamine analogues have been found (as expected). The impurities that have been found in our preparation will be compared to the found impurities of clandestine PMA preparations in the next chapter.

3.3. Impurities

3.3.1. Anethole

Anethole (4-methoxyphenyl-1-propene) has been used as precursor for its ketone PMP2P. The abundance of its presence depends on a variety of factors, such as intermediary distillation and purification steps. Also very important are the reaction time and temperature. Anethole has been found in most samples (HSPME and liquid–liquid extraction) that were taken from the beginning (anise oil itself) till the end of the PMA synthesis (PMA oil using Leuckart).

3.3.2. 4-Methoxyphenol

The presence of 4-methoxyphenol in PMA samples has been mentioned before [5]. Depending on the origin of the anise oil (country and species), a certain amount of

4-methoxybenzaldehyde can expected to be found. In our Leuckart PMA oil, there were traces of both 4-methoxybenzaldehyde and 4-methoxyphenol (GC-HSPME/MS).

The action of H_2O_2 on 4-methoxybenzaldehyde cannot be responsible for the production of 4-methoxyphenol, since this oxidation reaction (as well as auto-oxidation) would yield 4-methoxybenzoic acid (*p*-anisic acid). This has been confirmed via synthesis and by screening via GC/MS. Fifty milligram *p*-anisic acid crystals were dissolved in 5 ml MeOH and 1 μl was injected into GC/MS (split ratio 50:1). This revealed *p*-anisic acid being the main component and 4-methoxybenzaldehyde as impurity. The action of performic acid on 4-methoxybenzaldehyde could be responsible for the production of 4-methoxyphenol, this according to the Baeyer–Villiger rearrangement: ketones (or aldehydes) can be converted to esters using peracids as oxidizing agents [12,13]. This well-known reaction has been studied by Adolf Von Baeyer and Victor Villiger [14]. The Baeyer–Villiger oxidation of methoxybenzaldehydes in the preparation of methoxyphenols has been documented for peracetic and meta-chloroperbenzoic acid [15]. Theoretically, the action of performic acid on 4-methoxybenzaldehyde yields a formate ester, which will set free the 4-methoxyphenol after saponification with for instance NaOH (cf. Fig. 5). This has been verified by sampling of the DCM phase during the reaction. Fig. 6 shows the evolution of the reaction: one compound emerges while another one is depleted. chromatogram A in Fig. 6 shows the situation after 10 min (when 12.5% of the performic acid has been added): the major peak at 4.68 min consists of 4-methoxybenzaldehyde, while a small peak at 4.48 min consists of a compound which has been identified as 4-methoxyformylphenol ($C_8H_8O_3$, $M = 152$ g/mol). As can be derived from chromatograms B, C and D in Fig. 6, the relative abundance of the latter formate ester increases during the reaction. Samples taken near the end of the reaction show the presence of 4-methoxyphenol as well. The mass spectrum of 4-methoxyphenol can be found in Fig. 7 and shows similarities with the mass spectrum of 4-methoxyformylphenol, which can be seen in Fig. 6 chromatogram D. It should be noted that the essential oils of star anise sometimes contain trace amounts of 4-methoxyphenol, probably as glucosides [7e]. We didn't find

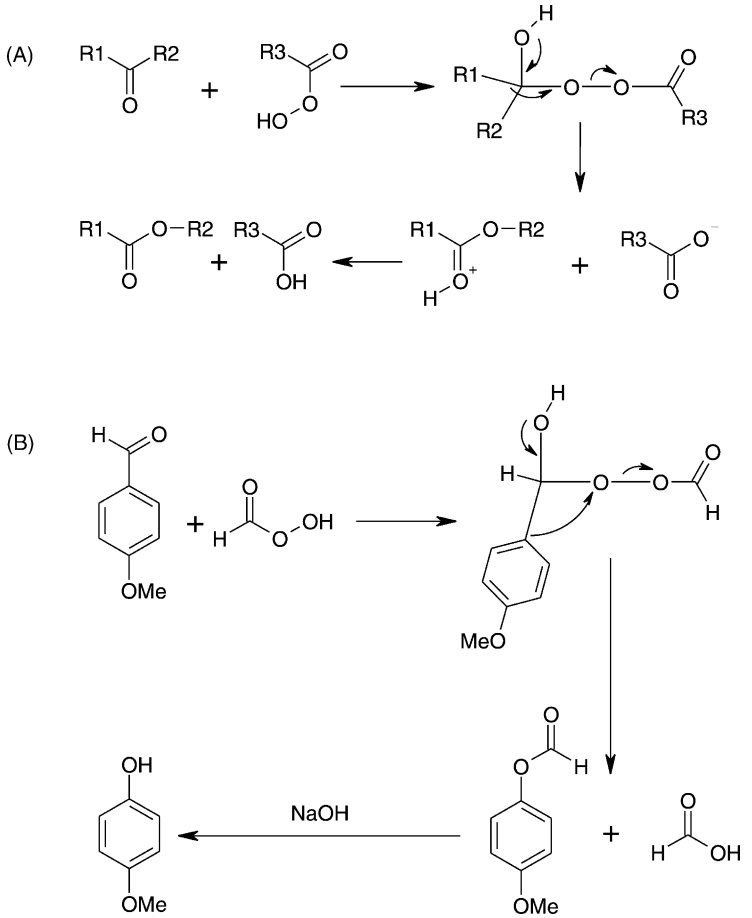

Fig. 5. (A) General scheme of the Baeyer–Villiger rearrangement; (B) the Baeyer–Villiger rearrangement applied to the reaction of 4-methoxybenzaldehyde with performic acid, followed by saponification with NaOH to set free 4-methoxyphenol.

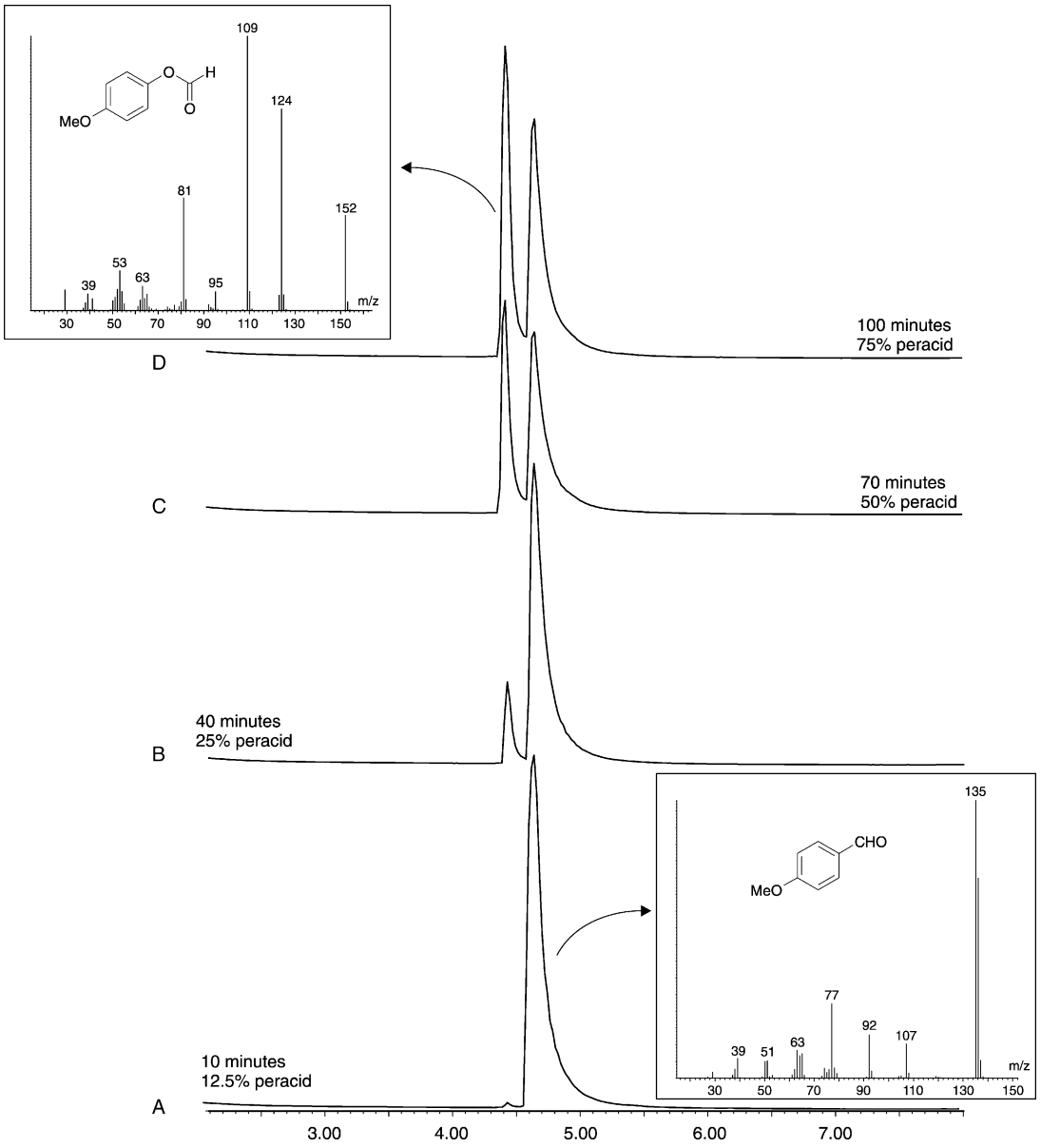

Fig. 6. GC-HSPME/MS chromatograms, split ratio (25:1): Part A includes the mass spectrum of 4-methoxybenzaldehyde, Part D shows the mass spectrum of 4-methoxyformylphenol.

4-methoxyphenol via GC-HSPME/MS in the anise oil we used as starting product (cf. Fig. 2).

We applied our findings on the synthesis of PMP2P, which has previously been explained. In the chromatograms A–D of Fig. 3, no trace of 4-methoxybenzaldehyde, 4-methoxyphenol or its formyl ether was found. In E and F, 4-methoxybenzaldehyde and 4-methoxyformylphenol are noticed. In a sample taken at the end of the performic reaction, there was 4-methoxyphenol present as well. The GC-HSPME/MS chromatogram of the undistilled PMP2P (cf. Fig. 4) displays 4-methoxybenzaldehyde, 4-methoxyphenol and traces of its formyl ether. It should be noticed that the anise oil we used as source did not contain any trace of 4-methoxybenzaldehyde.

3.3.3. 4-Methyl-5-(4-methoxyphenyl)pyrimidine (MMPP) and 4-(p-methoxybenzyl)pyrimidine (MBP)

MMPP is a 4-methyl-5-phenylpyrimidine derivative and has previously been described as a typical Leuckart impurity in the synthesis of PMA [1,5]. 4-Methyl-5-phenylpyrimidine has been reported for the first time by van der Ark et al. [16,17] as impurity in the Leuckart synthesis of ampheta-

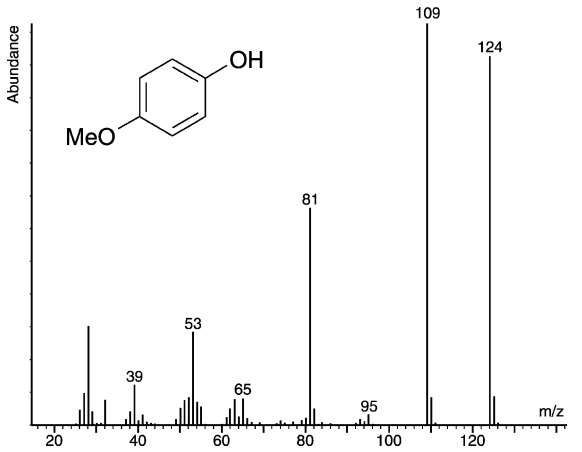

Fig. 7. Mass spectrum of *p*-methoxyphenol.

mine. Analogously to the formation of 4-methyl-5-phenylpyrimidine as suggested by van der Ark, MMPP is most likely formed by a series of three condensation reactions (cf. Fig. 8): PMP2P will condense with formamide to form *N*-formyl-1-(*p*-methoxyphenyl)-2-iminopropane. The latter will condense with another molecule of formamide to yield 2-(*p*-methoxybenzyl)-3,5-diaza-2,4-hexadiene-6-aldehyde, which will convert into MMPP via ring closure at the α-carbon relative to the phenyl group. Ring closure at the γ-carbon is possible as well, and will yield MBP. The latter has been reported by Kirkbride et al. [1] as well. Both pyrimidines have been found in PMA synthesized by us (applying GC-HSPME/MS). Theoretically, the formation of MMPP is preferred above MBP. The hydrogen atoms α to the phenyl group are more vulnerable than those in the γ position.

3.3.4. Ketimines and their reduced analogues

N-(β-4-Methoxyphenylisopropyl)-4-methoxybenzyl methyl ketimine is an imine formed by the condensation of PMP2P and PMA in the reaction mixture (cf. Fig. 9). It was tentatively identified by comparing its mass spectrum with an analogue compound from the clandestine amphetamine synthesis, viz. *N*-(β-phenylisopropyl)benzyl methyl ketimine (cf. Fig. 9). The mass spectrum of the latter shows three characteristic ions, namely $m/z = 91$, 119 and 160 [34], and the molecular ion $m/z = 251$. The mass spectrum of *N*-(β-4-methoxyphenylisopropyl)-4-methoxybenzyl methyl ketimine has characteristic ions at $m/z = 121$, 149 and 190, and the molecular ion $m/z = 311$. Based on the

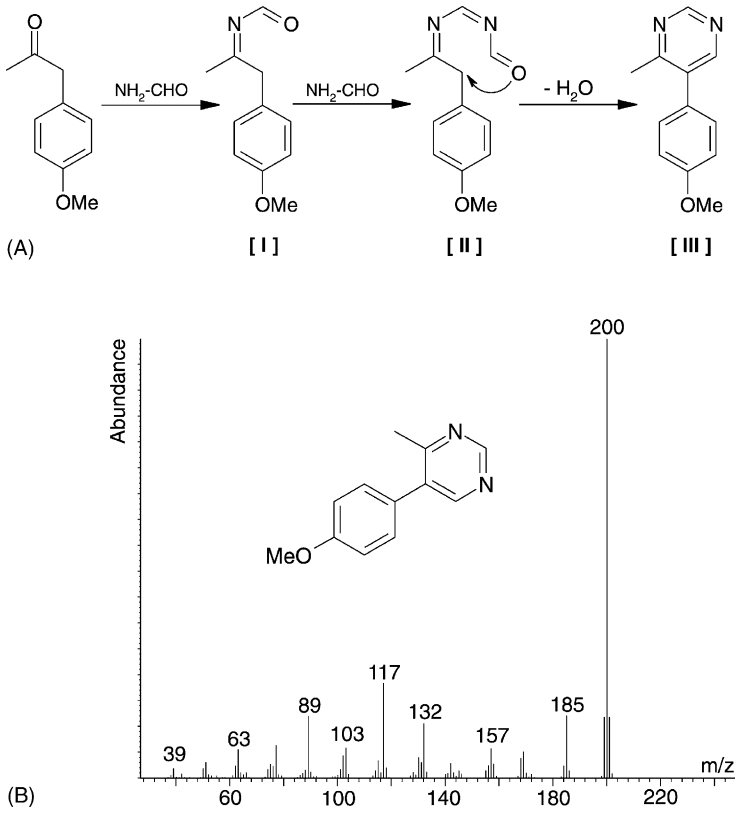

Fig. 8. (A) Hypothetical reaction path for MMPP: PMP2P will condense with formamide to yield *N*-formyl-1-(*p*-methoxyphenyl)-2-iminopropane [I]. This molecule condenses with another formamide molecule to 2-(*p*-methoxybenzyl)-3,5-diaza-2,4-hexadiene-6-aldehyde [II], which can convert to MMPP [III] by ring closure (drawing according to van der Ark et al. [16]); (B) mass spectrum for MMPP.

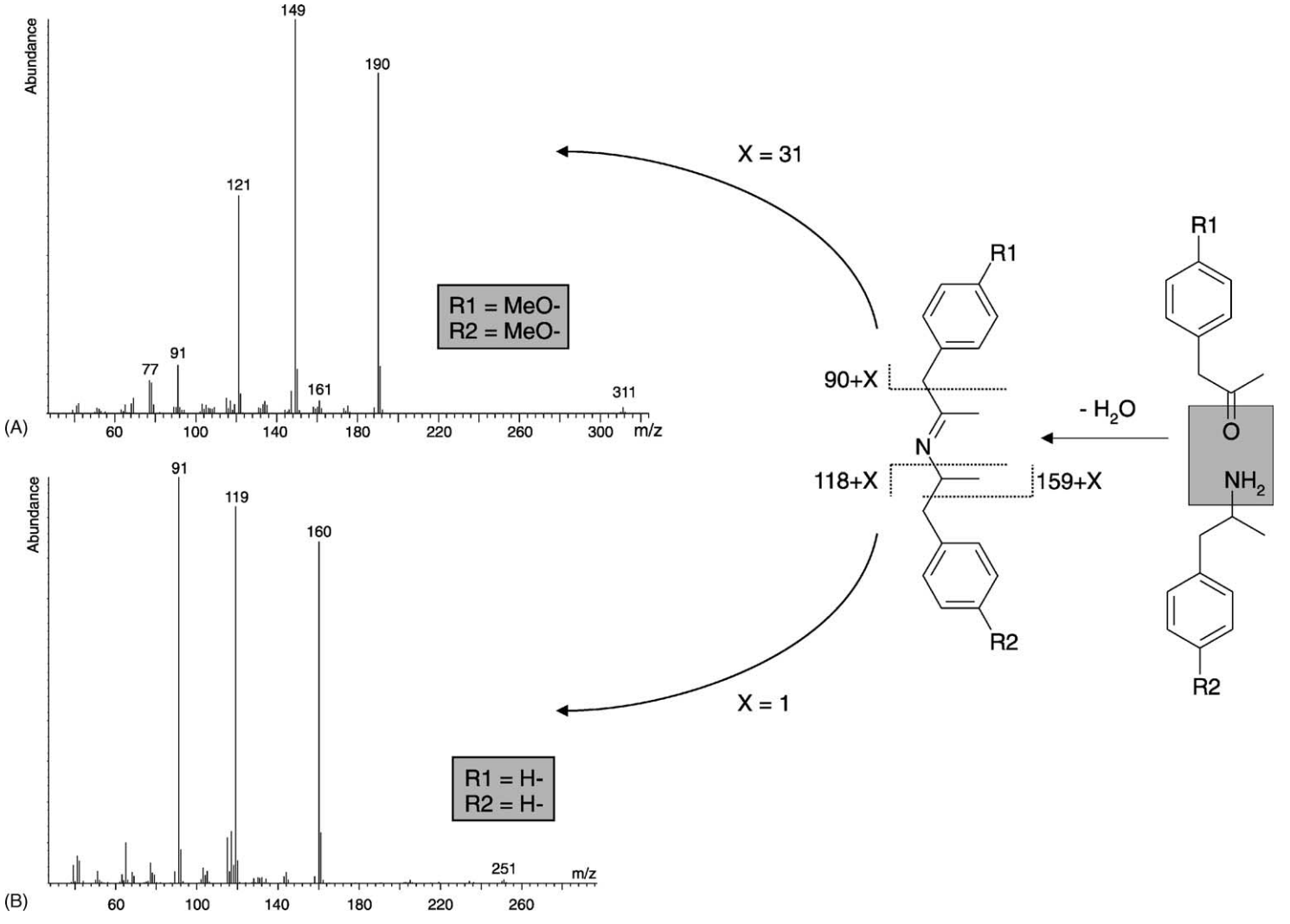

Fig. 9. (A) Mass spectrum for *N*-(α-4-methoxyphenylisopropyl)-4-methoxybenzyl methyl ketimine; (B) mass spectrum for *N*-(α-phenylisopropyl) benzyl methyl ketimine. The condensation reaction between PMA and its ketone PMP2P is presented at the right.

molecular structures, the three characteristic ions should have $m/z = 90 + X$, $118 + X$ and $159 + X$, where X is the mass of a substituent on the phenyl rings. For *N*-(β-phenylisopropyl)benzyl methyl ketimine, $X = 1$ (hydrogen), while for *N*-(β-4-methoxyphenylisopropyl)-4-methoxybenzyl methyl ketimine, $X = 31$ (methoxy). Substituents on the phenyl ring can have an influence on the abundance ratio of the three characteristic ions [18]. This substance has recently been tentatively identified by Blachut et al. [6] as well. The ketimine formed by condensation of 4-methoxybenzaldehyde and PMA, of *N*-(β-4-methoxyphenylisopropyl)-4-methoxybenzaldimine, has been tentatively identified in a similar way and is also reported by Blachut et al. [6]. Both ketimines have been found in our PMA preparation, as well as in the clandestine samples (via liquid–liquid extraction).

1-(4-Methoxyphenyl)-*N*-(2-(4-methoxyphenyl)-1-methylethyl-2-propanamine and 1-(4-methoxyphenyl)-*N*-methyl-*N*-(2-(4-methoxyphenyl)-1-methylethyl-2-propanamine are two impurities that have been recently identified by Blachut et al. [6] and have been retrieved in our and clandestine PMA preparations (via liquid–liquid injection). They are formed by reduction of the imine analogue. The *N*-formyl derivative has not been found. The two substances are indications for the application of the Leuckart reaction.

3.3.5. Essential oil related impurities

The characterization of essential oils is not a simple task, since essential oils from the same plant species can have a different composition, usually depending on the origin of the plant (climate, soil condition, harvesting time etc.) and the age of the oil. Though it is hard to say whether anise oil originates from anise or star anise solely based on chromatograms, GC-HSPME/MS analysis can reveal very useful information for the forensic investigator. Substances as borneol, camphor, limonene and other terpenes have been found in our and various confiscated PMA preparations using this method. Since these substances are typically present in the essential oils of plants and should not be present in used solvents and/or reagents, their presence can be an indication for the use of essential oils as starting product.

4. Conclusion

MDMA is currently one of the most popular drugs of abuse. Since its precursors are watched by government organizations, underground chemists search for alternatives. In our case, we presented such an alternative: the synthesis of PMA using anethole, a main constituent of anise oil, as precursor. Although PMA itself is a regulated substance, its precursors are currently unscheduled and easy obtainable. From this angle, PMA is a serious threat. The usefulness of anise oil as precursor has been demonstrated by synthesizing PMP2P using the performic acid pathway. We also showed that 4-methoxyphenol is formed from 4-methoxybenzaldehyde via the Baeyer–Villiger reaction during the performic reaction. Additionally, we retrieved several Leuckart-specific impurities, which have recently been described in the literature [1,5,6]. Furthermore, we proved that GC-HSPME/MS could be a useful technique in constructing impurity profiles.

References

[1] K.P. Kirkbride, A.D. Ward, N.F. Jenkins, G. Klass, J.C. Coumbaros, Synthesis of 4-methyl-5-arylpyrimidines and 4-arylpyrimidines: route specific markers for the Leuckardt preparation of amphetamine, 4-methoxyamphetamine, and 4-methylthioamphetamine, Forensic Sci. Int. 115 (2001) 53–67.

[2] M. Weise, Das traurige Ende einer "Geburtstagsfeier"—Fatale Intoxikation mit 4-methylthioamphetamin. Kasuistik aus dem Arbeitskreis Klinische Toxikologie, Toxichem. Krimtech. 68 (2001) 38–42.

[3] A.J. Poortman, E. Lock, Analytical profile of 4-methylthioamphetamine (4-MTA), a new street drug, Forensic Sci. Int. 100 (1999) 221–233.

[4] A. Shulgin, A. Shulgin, PiHKAL: A Chemical Love Story, First ed., Transform Press, Berkeley, 1998 (4th printing) (a) pp. 707–709, (b) p. 783, (c) pp. 860–861.

[5] J.C. Coumbaros, K.P. Kirkbride, G. Klass, Application of solid-phase microextraction to the profiling of an illicit drug: manufacturing impurities in illicit 4-methoxyamphetamine, J. Forensic Sci. 44 (1999) 1237–1242.

[6] D. Blachut, K. Wojtasiewicz, Z. Czarnocki, Identification and synthesis of some contaminants present in 4-methoxyamphetamine (PMA) prepared by the Leuckart method, Forensic Sci. Int. 127 (2002) 45–62.

[7] E. Guenther, The Essential Oils, D. Van Nostrand Company, New York, 1950, (a) vol. 4, pp. 563–570 and pp. 634–645, (b) vol. 5, pp. 361–379, (c) vol. 4, pp. 459–463, (d) vol. 4, pp. 506–508, (e) vol. 2, p. 551.

[8] V. Meyer, P. Jacobson, Lehrbuch der Organischen Chemie, Walter de Gruyter & Co., Berlin, 1923, B II T I, pp. 432–433.

[9] M. Gloger, H. Neumann, Analyse von Heroinproben mit der Kapillargaschromatographie. Vergleich von Glaskapillartrennsäule und gepackter Säule, Forensic Sci. Int. 22 (1983) 63–74.

[10] T.A. Dal Cason, S.A. Angelos, J.K. Raney, A clandestine approach to the synthesis of phenyl-2-propanone from phenylpropenes, J. Forensic Sci. 29 (1984) 1187–1208.

[11] C.R. Clark, F.T. Noggle, J. DeRuiter, S. Andurkar, GC-MS analysis of products, intermediates and by-products in the synthesis of MDA from isosafrole, Microgram 27 (1994) 188–200.

[12] J.D. Roberts, M.C. Caserio, Basic Principles of Organic Chemistry, W.A. Benjamin Inc., New York, 1965, p. 557.

[13] S. Moulay, The most well-known rearrangements in organic chemistry at hand, Chem. Educ. Res. Pract. Eur. 3 (2002) 33–64.

[14] Adolf Von Baeyer's Gesammelte Werke, Herausgegeben zur Feier des siebzigsten Geburtstages des Autors, Friedrich Vieweg und Sohn, Braunschweig, 1905, pp. 711–808.

[15] I.A. Godfrey, M.V. Sargent, Preparation of methoxyphenols by Baeyer–Villiger oxidation of methoxybenzaldehydes, J. Chem. Soc., Perkin Trans. I 10 (1974) 1353–1354.
[16] A.M. Van Der Ark, A.B.E. Theeuwen, A.M.A. Verweij, Impurities in illicit amphetamine. 1. Isolation and identification of some pyrimidines, Pharmaceutisch Weekblad 112 (1977) 977–979.
[17] A.M. van der Ark, A.M.A. Verweij, A. Sinnema, Weakly basic impurities in illicit amphetamine, J. Forensic Sci. 23 (1978) 693–700.
[18] P.A. Weibel, M. Hesse, Substituenteneinfluss bei der massenspektrometrischen Fragmentierung: Untersuchungen an *N*-methyl-β,β′-diphenyl-diäthylaminen, Helv. Chim. Acta 56 (1973) 2460–2479.