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A study of impurities in intermediates and 3,4-methylenedioxymethamphetamine (MDMA) samples produced via reductive amination routes

P. Gimeno, F. Besacier*, M. Bottex, L. Dujourdy, H. Chaudron-Thozet

Laboratoire de Police Scientifique de Lyon, 31 Avenue Franklin Roosevelt, 69134 Ecully, France

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Abstract

Impurities found in various sources of precursors (sassafras oil, safrol, isosafrol, piperonal), intermediates (β-nitroisosafrol, piperonylmethylketone (PMK)) and final product (3,4-methylenedioxymethamphetamine (MDMA)) are presented and discussed. Particular attention is paid to the chemical origin of each impurity found in the prepared samples. Impurity profiles of isosafrol, piperonal, and PMK samples obtained from industrial sources or from sassafras oil were first compared. Then PMK samples produced from isosafrol through isosafrol glycol or through β-nitroisosafrol were compared. At last, attention was paid to the reductive amination of PMK to MDMA using different reductive agents. Possible use of this profiling method to determine the synthesis route is discussed for all products.

Keywords: 3,4-Methylenedioxymethamphetamine (MDMA); Impurities; Gas chromatography; Mass spectrometry; Reductive amination

1. Introduction

Most of the synthesis routes leading to 3,4-methylenedioxymethamphetamine (MDMA) start with materials that contain the preformed methylenedioxyphenyl ring, e.g. safrol, piperonal, isosafrol, and piperonylmethylketone (PMK). They often proceed via the PMK intermediate, which could be converted into MDMA using two methods: (i) Leuckart's reaction and (ii) reductive amination, the last one being the predominant one. Clandestine manufacturing of MDMA analogs and homologs has been discussed from a global point of view by Dal Carson [1]. MDMA samples contain precursors, intermediates and other trace level impurities whose characterization might assist in establishing the synthesis route used [2,3]. Therefore, structure elucidation of MDMA impurities was studied for various routes: reductive amination [4], nitropropene [5], Leuckart [5,6], or bromopropane [6,7]. Besides, some authors focused on the analysis of impurities found in illicit tablets [8–13] and tried to correlate them to a specific synthesis route.

In a previous study, we analyzed numerous MDMA tablets seized by the French Police and found that reductive amination was the predominant route used [14]. Therefore, we decided to focus on that particular route and conducted various syntheses: synthesis of PMK via the glycol route (from isosafrol) and the nitrostyrene route (from piperonal) and then conversion to MDMA, synthesis of MDMA from PMK using different reduction agents ($NaBH_4$, $NaBH_3CN$, Al–Hg amalgam).

The objective was to identify the impurities at each stage and then assess if the profiling method allowed determining the whole chemical pathway of MDMA from the precursor (isosafrol or piperonal) to the reduction agent.

* Corresponding author. Tel.: +33 47 286 8982.
E-mail address: Fabrice.Besacier@interieur.gouv.fr (F. Besacier).

2. Materials and methods

2.1. Gas chromatography and mass spectrometry

All analyses were carried out on a Thermofinnigan GC trace 2000 gas chromatograph interfaced with an ion trap Polaris mass spectrometer. Two microliters of each extract were injected according to the splitless mode using a Thermofinnigan AS 2000 autosampler. The column was a Supelco PTA5 capillary column (crosslinked poly 5% diphenyl/95% dimethylsiloxane); 30 m × 0.32 mm (i.d.) × 0.5 μm film thickness. The oven temperature was programmed as follows: 50 °C for 1 min, 5 °C min^{-1} to 150 °C for 12 min, and 15 °C min^{-1} to 300 °C for 10 min. The injection port and transfer line temperatures were 280 °C and 275 °C, respectively. The ion source temperature was set at 200 °C, and the helium carrier gas flow rate was fixed at 1 ml min^{-1}. The mass spectrometer was tuned on electron impact ionization (Ei) for low-mass analysis for detection of each impurity. In order to preserve the MS filament life, the mass spectrometer was switched off during elution of the major compounds.

2.2. Materials

Safrole (97%), *cis* and *trans* mixture of isosafrole (95%), piperonal (99%), methylamine HCl (98%) and nitroethane (98%) were purchased from Acros Organics (NJ, USA). Sassafras oil (from Vietnam) was obtained from Hevea (renamed LBVH, Vallauris, France). Reductive agents were: $NaBH_3CN$ (95%) from Aldrich (St. Quentin Fallavier, France), $NaBH_4$ (98%) from Acros Organics and $HgCl_2$ (99.5%) from Prolabo (Fontenay sous bois, France). Oxidative compounds ($Na_2Cr_2O_7$ and H_2O_2) were from Janssen Chimica and Acros Organics, respectively. Catalysts: aliquot 336 (99%), iron (98%) and cyclohexylamine (99%) came from Janssen chimica, Laurylab (St. Fons, France) and Acros Organics, respectively. All organic solvents (more than 99%), acids and bases were obtained from different industrial sources.

2.3. Standard extraction method

Ten milligram or 10 μl of sample were weighed and dissolved into 2 ml of a buffer solution at pH 11.5 and shacked for 10 min at 1800 rpm. The extraction was performed adding 3 ml of diethylether and shaking for another 10 min. After centrifugation, the organic layer was transferred to a conic tube and evaporated to dryness under monitored conditions at room temperature (extracts were evaporated to dryness under a low nitrogen flow rate). Five microliters of diethylether containing an ISTD were added to the tube, shacked for a few seconds, and transferred to a micro-vial for profile analysis. In order to avoid impurity degradation, the extracts were injected the same day they were prepared.

3. Syntheses, analysis and discussion

3.1. Study of PMK

Two synthesis routes were studied (see [1] for relevant references):

- Route I allowed PMK synthesis from isosafrol through the intermediate isosafrol glycol (Scheme 1). In Route Ia, pure isosafrol from Acros Organic was used, whereas in Route Ib, it was obtained by isomerization of safrol extracted from sassafras oil.
- Route II involved the formation of β-nitroisosafrol obtained via the Knoevenagel–Walter condensation of piperonal with nitroethane, followed by hydrolysis of the intermediate oxime to give PMK (Scheme 2). In Route IIa, pure piperonal from Acros Organic was used, whereas in Route IIb, it was obtained by oxidation of pure isosafrol.

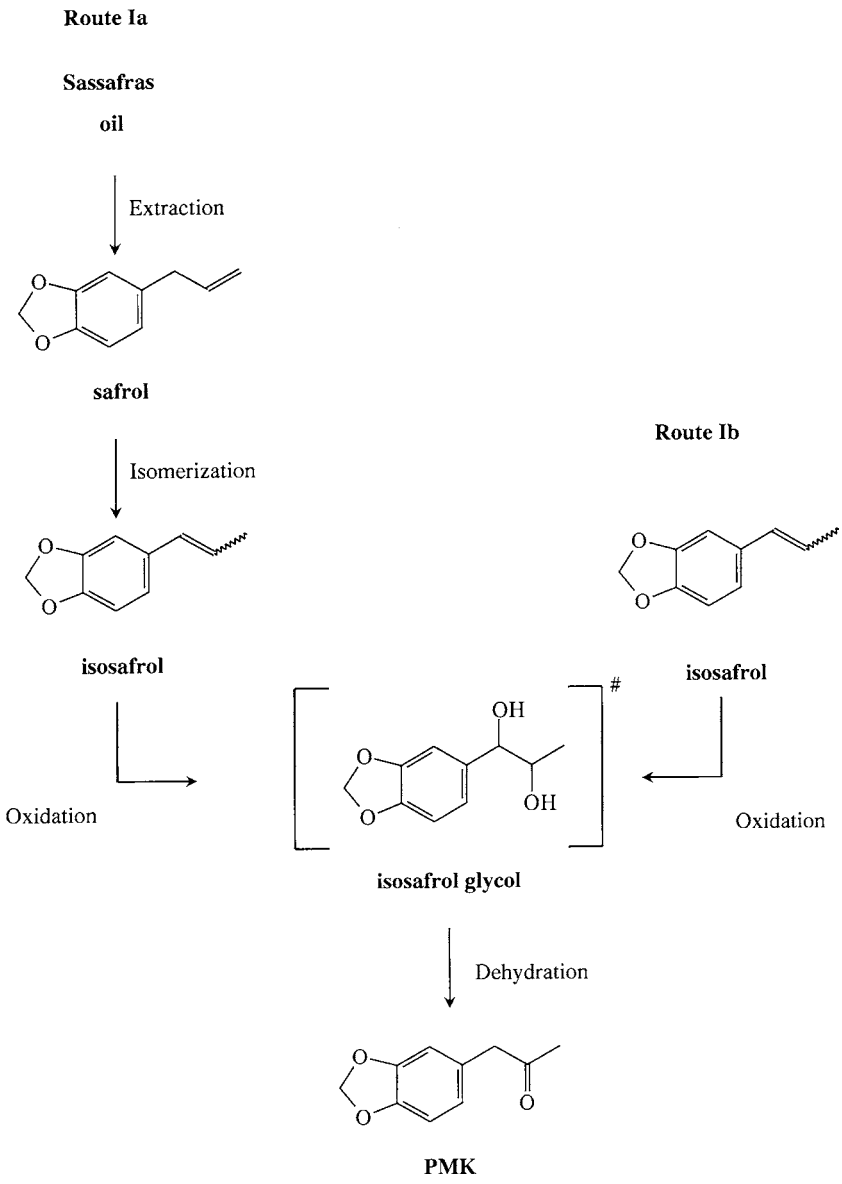
3.1.1. Syntheses

3.1.1.1. Safrol (Route Ib). Safrol was isolated from sassafras oil by extraction with water and purified by low-pressure distillation.

3.1.1.2. Isosafrol (Route Ib). To 20 g of safrol were added 8.3 g of solid KOH and 3 g of aliquot 336 (phase transfer catalyst). After a vigorous shaking (20 min) at room temperature, the mixture was left at 80 °C within 1 h 15 min. After cooling to room temperature, the mixture was diluted with 500 ml of methylene chloride and filtered through celite. The filtrate was then dried ($MgSO_4$) and concentrated by a rotary evaporation. The crude product was then purified in vacuum to yield 14.9 g (75%) of isosafrol as colorless oil.

3.1.1.3. PMK (Routes Ia and Ib). To a well stirred solution of 29 g of 35% hydrogen peroxide in 136 g of formic acid (88%) and 20.5 g of water, is added dropwise to a solution of 32.4 g isosafrol (from sassafras oil – Route Ia – or from an industrial source – Route Ib) in 120 ml acetone, with cooling to keep the mixture from exceeding 40 °C. After stirring for 16 h at room temperature, the mixture was concentrated under vacuum without heating. The crude product was dissolved in 55 ml of methyl alcohol, treated with 240 g of 15% sulfuric acid and heated for 3 h. After cooling, the reaction mixture was extracted with diethyl ether. Organic layers were washed with water and then with dilute sodium hydroxide. Solvent was removed by rotary evaporation. The residue was distilled under vacuum to provide 17.4 g (50%) of PMK as pale yellow oil.

3.1.1.4. Piperonal (Route IIb). A mixture of 28.1 g of an industrial source of isosafrol, 55.2 g of concentrated sulfuric acid, 600 ml of water and 9.6 g of sulfanilic acid (as dispersing agent) was vigorously stirred during addition over

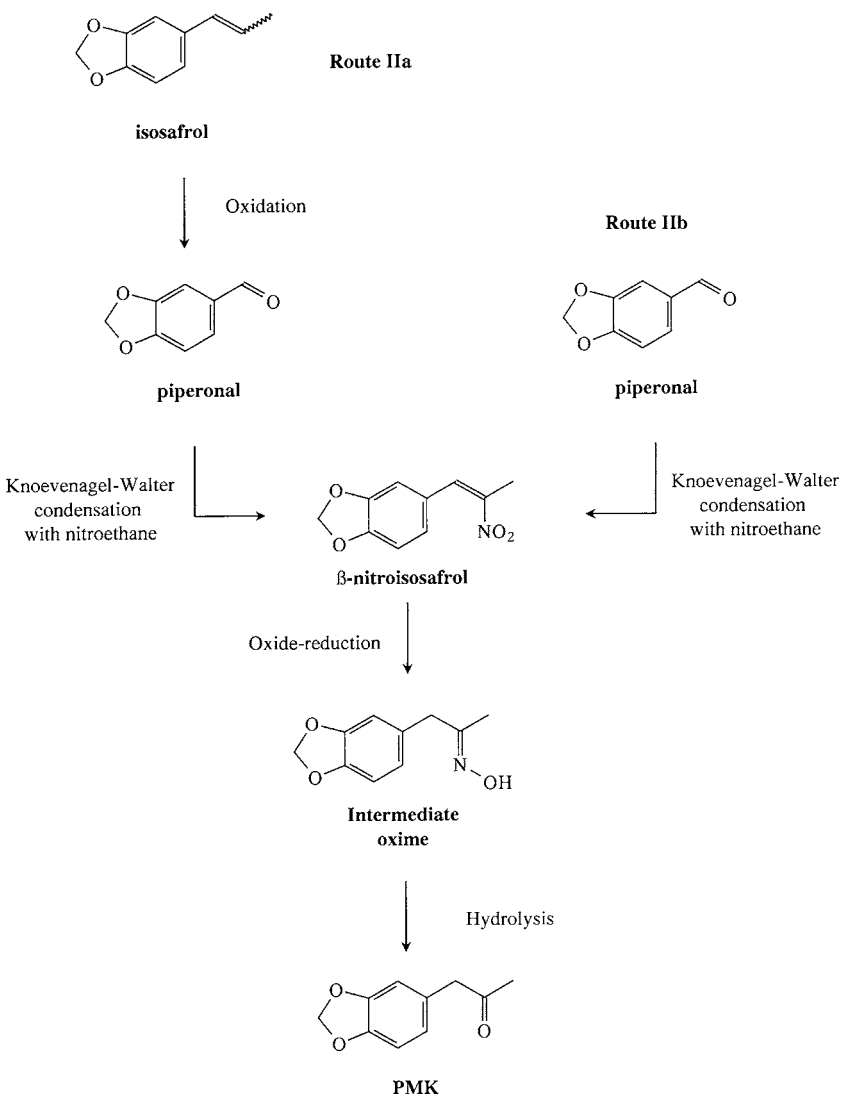


Scheme 1.

45 min of a solution of 30.2 g sodium dichromate in water (140 ml). Stirring was then continued for 1 h at 40 °C (without external heating). After cooling, the mixture was extracted with toluene. The combined extracts were washed with dilute sodium hydroxide followed by water, dried over $MgSO_4$ and concentrated in vacuum. Piperonal (10.2 g, 55%) was obtained in white crystals from the crude product cooled in ice bath.

3.1.1.5. β-Nitroisosafrol (Routes IIa and IIb). To a solution of 9 g of piperonal (from industrial source – Route IIa – or from synthesis – Route IIb) in 47 ml glacial acetic acid, treated with 9.25 g of nitroethane, were added dropwise at 5 °C, 6.2 g cyclohexylamine. The mixture was then held to reflux temperature for 6 h. After addition of 10 ml water followed by cooling, crude β-nitroisosafrol was removed by filtration, recrystallized in 110 ml methanol and dried to provide 5 g (40%) of bright yellow crystals.

3.1.1.6. PMK (Route IIa and IIb). 4.5 g of β-nitroisosafrol were dissolved in 65 ml acetic acid and added to a well



Scheme 2.

Table 1a
Common impurities found in safrol from a natural (sassafras oil) or an industrial source

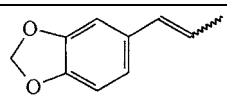
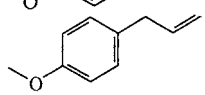
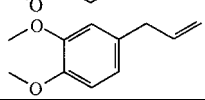
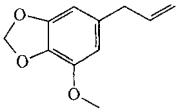
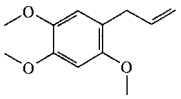
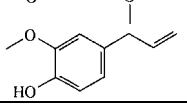
Identification number	*m/z*	Structure	Name	Note
4iso	162, 104, 131, 77, 51		Isosafrol, MW 162	Both isomers detected
7saf	148-147-117-133-105-91-77		1-Methoxy-4-(2-propeny 1)-benzene, MW 148	
8saf	178-163-107-91-103-77		1,2-Dimethoxy-4-(2-propenyl)-benzene, MW 178	

Table 1b
Impurities only detected in safrol extracted from sassafras oil

Identification number	*m/z*	Structure	Name	Note
17saf	192, 193, 165, 119, 91		4-Methoxy-6-(2-propenyl)-1,3-benzodioxole, MW 192	
18saf	208, 193, 165, 69, 91		1,2,4-Trimethoxy-5-(1-propenyl)-benzene, MW 208	
19saf	164, 165, 149, 77, 103		Eugenol, MW 164	

stirred suspension of 14.5 g elemental iron in 65 ml warm acetic acid. The mixture was heated to reflux for 2 h and then cooled to room temperature. After removing excess iron by filtration, 800 ml of water was added. The aqueous layer was then extracted with methylene chloride, the extracts pooled and washed with diluted sodium hydroxide followed by water, dried over $MgSO_4$ and the solvent was removed in vacuum. Distillation of the residue yields 2 g (56%) of PMK.

Table 2a
Common impurities found in isosafrol from safrol or industrial source (Routes Ia and Ib)

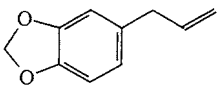
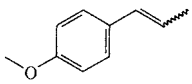
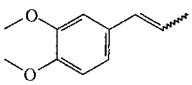
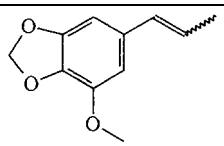
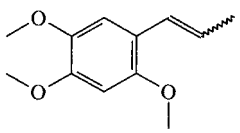
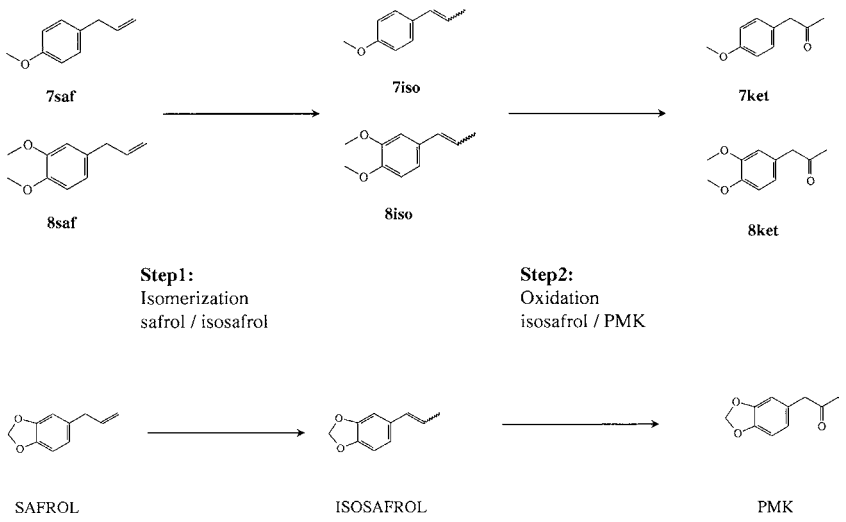
Identification number	*m/z*	Structure	Name	Note
3saf	162, 104, 131, 77, 51		Safrol, MW 162	Precursor
7iso	148-147-117-133-105-91-77		1-Methoxy-4-(1-propenyl)-benzene, MW 148	Total isomerization of impurity 7saf. Both isomers detected
8iso	178-163-107-91-103-77		1,2-Dimethoxy-4-(1-propenyl)-benzene, MW 178	Total isomerization of impurity 8saf. Both isomers detected

Table 2b
Impurities only detected in isosafrole from safrol (Route Ia)

Identification number	*m/z*	Structure	Name	Note
17iso	192-165-91-119-65		1,2-Methylenedioxy-3-methoxy-5-(1-propenyl)-benzene, MW 192	Total isomerization of impurity 17saf. Both isomers detected
18iso	208-193-165-91-137		1,2,4-Trimethoxy-5-(1-propenyl)-benzene, MW 208	Total isomerization of impurity 18saf. Both isomers detected



Scheme 3.

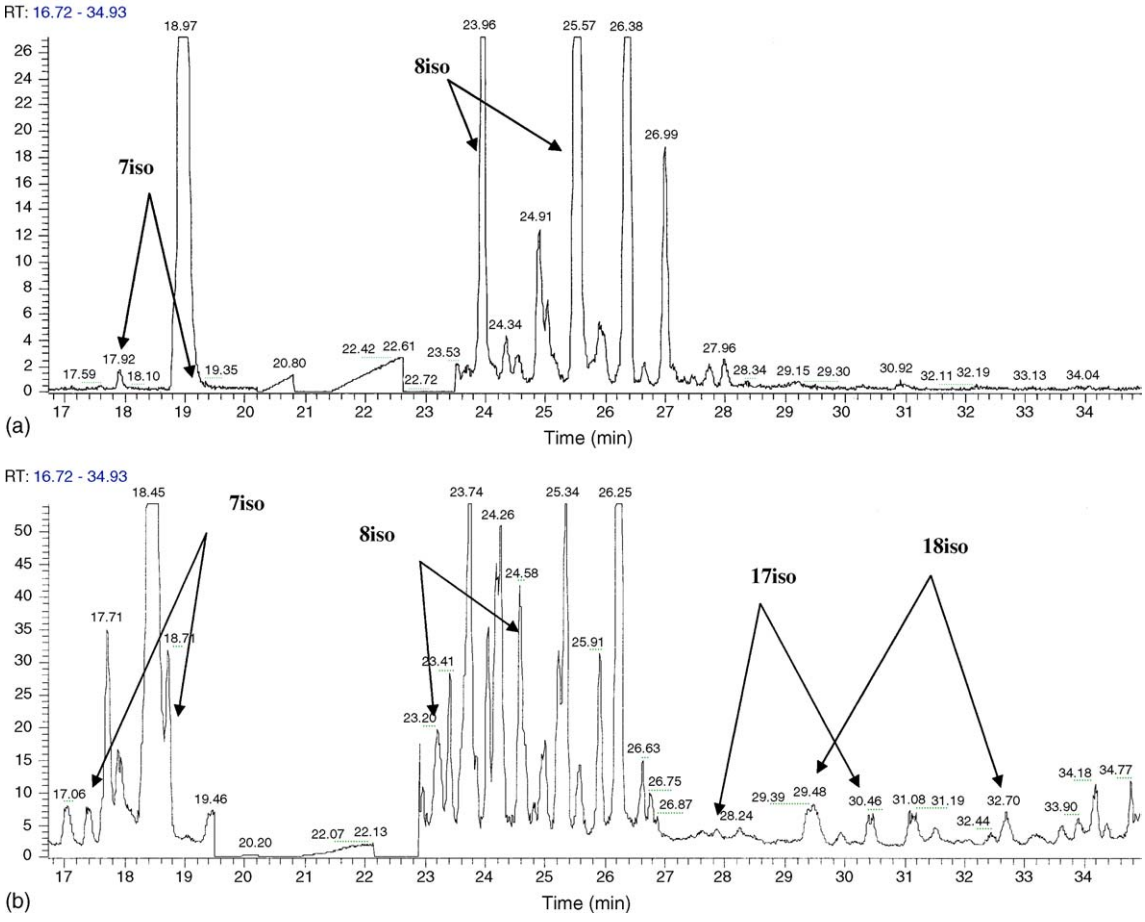
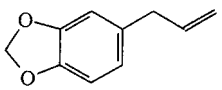
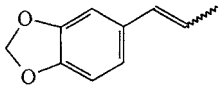
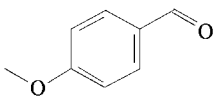
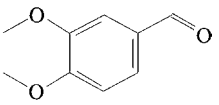


Fig. 1. Chromatograms of isosafrol samples, (a) industrial source (Route Ia), (b) from safrol (Route Ib).

Table 3a
Common impurities found in piperonal samples (Routes IIa and IIb)

Identification number	*m/z*	Structure	Name	Note
3saf	162, 104, 131, 77, 51		Safrol, MW 162	Precursor
4iso	162, 104, 131, 77, 51		Isosafrol, MW 162	Precursor
7pip	135/136, 77, 107, 92		4-Methoxy-benzaldehyde, MW 136	Complete oxidation of 7iso Very weak in the puchased sample
8pip	166/165, 151, 95, 77		3,4-Dimethoxy-benzaldehyde, MW 194	Complete oxidation of 8iso Very weak in the purchased sample

3.1.2. Analysis of safrol and isosafrol samples

Common impurities detected in safrol or isosafrol regardless the sources are shown in Table 1a and Table 2a, respectively. Additional impurities not present in the industrial samples are shown in Table 1b (safrol) and Table 2b (isosafrol). These last impurities are easily explained by the difference of purification between the purchased samples and the home made ones.

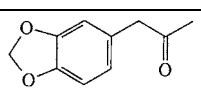
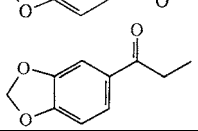
As we can notice in Tables 1a and 2a, some impurities completely react and are transformed during the different synthesis steps. For instance, impurities 7saf and 8saf were isomerized in 7iso and 8iso during the isomerization of safrol to isosafrol (Scheme 3). Two other ones 17iso and 18iso (Table 2b and Fig. 1) resulting from 17saf and 18saf are particularly interesting as they are only present in Route Ib, i.e. sassafras route.

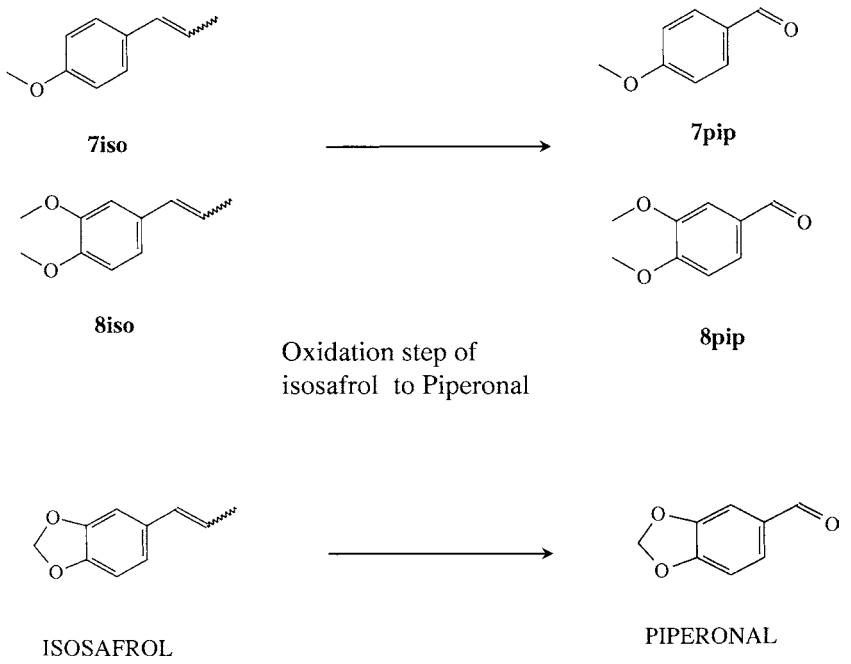
3.1.3. Analysis of piperonal and β-nitroisosafrol samples

Common impurities detected in piperonal regardless of the source (from isosafrol or an industrial source) are shown in Table 3a. Additional impurities found in the synthesized sample are reported in Table 3b. It is interesting to notice that impurities 7pip and 8pip, resulting from oxidation of 7iso and 8iso during the oxidation of isosafrol (Scheme 4) are also detected in the purchased piperonal even at a very low amount. In both cases, piperonal was probably obtained from isosafrol but the purification step was more efficient for the purchased sample. Two impurities are also noticeable 6ket and 20ket, which come from a mild oxidation of isosafrol during the piperonal synthesis step (Scheme 5). Therefore, PMK is already appearing at this stage.

All impurities found in the β-nitroisosafrol sample are reported in Table 4. As we can notice, in addition to the precursors used in the earlier steps (5ket, 4iso, 3saf) unexpected impurities were found, like 1-(3,4-methylenedioxyphenyl)-2-propanone oxime (21nitro). This impurity is known to be produced during the oxido–reduction of β-nitroisosafrol to PMK. Detecting it so early in the synthesis is rather surprising.

Table 3b
Impurities only found in the piperonal sample obtained from Route IIb

Identification number	*m/z*	Structure	Name	Note
6ket	135, 178, 77, 51, 43		PMK, MW 178	Mild oxidation of isosafrol
20ket	149, 178, 121, 65, 91		3,4-Methylenedioxy propiophenone, MW 178	Mild oxidation of isosafrol



Scheme 4.

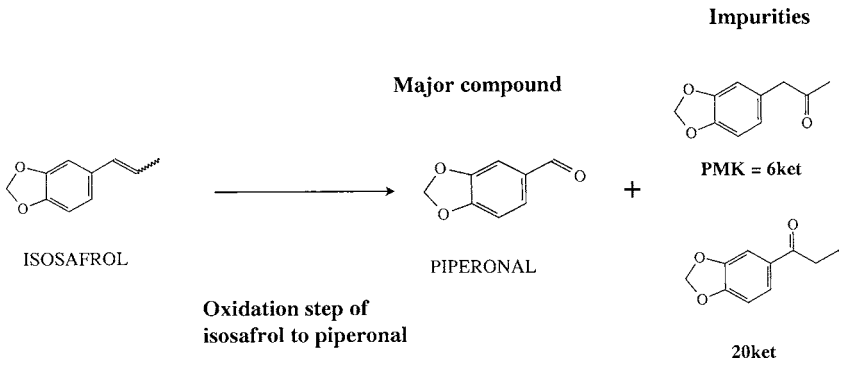
3.1.4. Analysis of PMK samples

Impurities detected in PMK depending on the synthesis route (Route I or II) are reported in Table 5. As we can notice in Tables 1a, 2a and 5, some impurities completely react and are transformed during the whole synthesis pathway. For instance, impurities 7saf and 8saf were isomerized to 7iso and 8iso during the isomerization of safrol to isosafrol, and then oxidized to 7ket and 8ket during the synthesis of PMK from isosafrol (Scheme 3).

Moreover, to distinguish the synthesis routes, it can be seen in Fig. 2 that for Route II impurity 7ket is present in a very weak amount, and 8ket not present at all. As a matter of fact, it is a three-step synthesis (Scheme 2) whereas Route I is a single step one (Scheme 1). Starting with the same impurities, an increase in steps means obviously a decrease in amounts.

Distinguishing synthesis Routes Ia and Ib, even if possible at an earlier stage (isosafrol), seems no longer possible. The specific impurities 17iso and 18iso are not converted into their corresponding oxidized products (17ket and 18ket) during the PMK synthesis, certainly due to their extremely weak amounts.

At last, it is important to point out that even if impurities 5ket and 20ket are detected in all PMK samples regardless of the synthesis route their chemical pathways are different. For Route I, 5ket (piperonal) is a by-product of



Scheme 5.

Table 4
Impurities found in β-nitroisosafrol

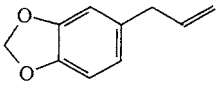
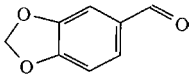
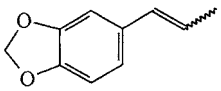
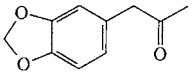
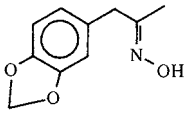
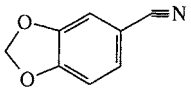
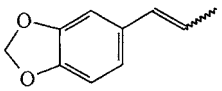
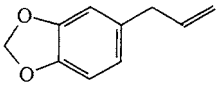
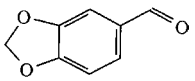
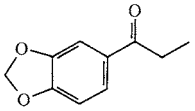
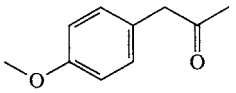
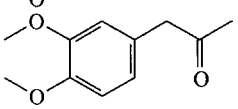
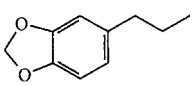
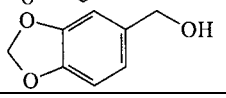
Identification number	*m/z*	Structure	Name	Note
3saf	162, 104, 131, 77, 51		Safrol, MW 162	Precursor
5ket	149/150, 121, 63, 91		Piperonal, MW 150	Precursor
4iso	162, 104, 131, 77, 51		Isosafrol, MW 162	Precursor both isomers detected
6ket	135, 178, 77, 51, 43		PMK, MW 178	Impurity already detected in piperonal
21nitro	165, 122, 63		1-(3,4-Methylenedioxyphenyl)-2-propanone oxime, MW 193	Unexplained origin
22nitro	146, 147, 62		Piperonylonitrile, MW 147	Unexplained origin

Table 5
Impurities found in the PMK samples depending on the synthesis route

Identification number	*m/z*	Structure	Name	Route I	Route II	Note
4iso	162, 104, 131, 77, 51		Isosafrol, MW 162	++	++	Precursor both isomers detected
3saf	162, 104, 131, 77, 51		Safrol, MW 162	++	++	Precursor
5ket	149/150, 121, 63, 91		Piperonal, MW 150	++	++++	Different origins depending on the route
20ket	149, 178, 135, 65		3,4-Methylenedioxy propiophenone, MW 178	++	Ø	Different origins depending on the route
7ket	121-164-77-91		1-(4-Methoxypherty 1)-2-Propanone, MW 178	++	+	Complete oxidation of 7iso
8ket	151-194-107-135		3,4-Dimethoxypheny lacetone, MW 194	++	Ø	Complete oxidation of 8iso
10meth	135, 164, 77, 51		Dihydrosafrol, MW 164	++	++	Safrol, or isosafrol reduction
11meth	152, 135, 93, 65, 123		Piperonyl alcohol, MW 152	++	++	Piperonal reduction

The symbols (+/++) refer to the intensities of the peak and (Ø) means nothing detectable.

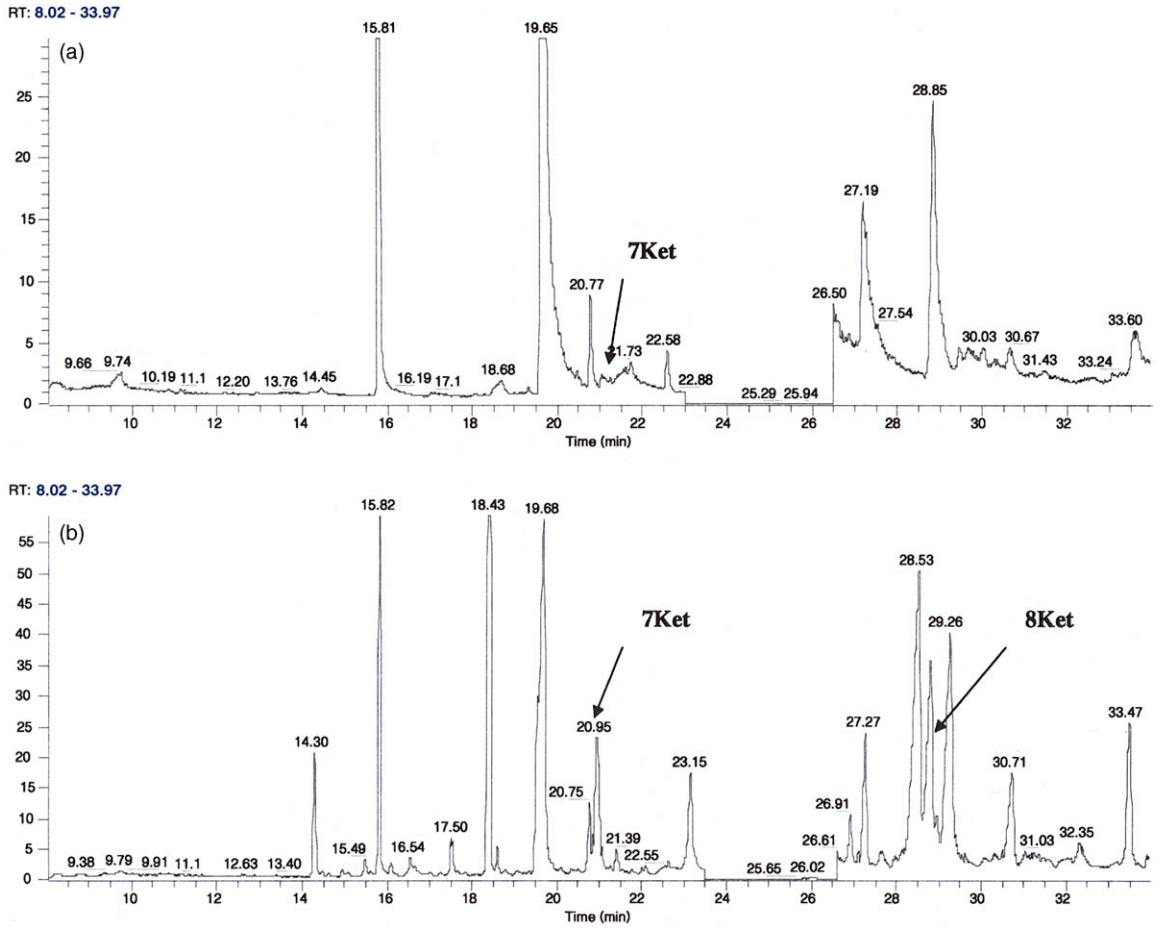
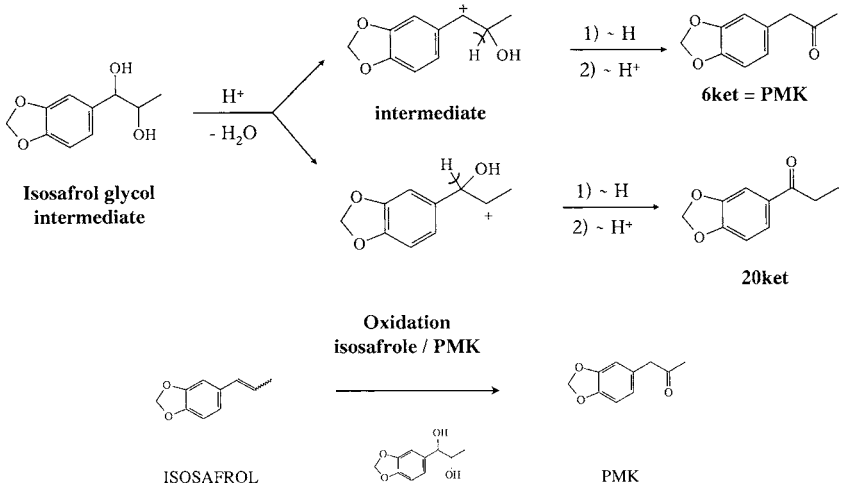
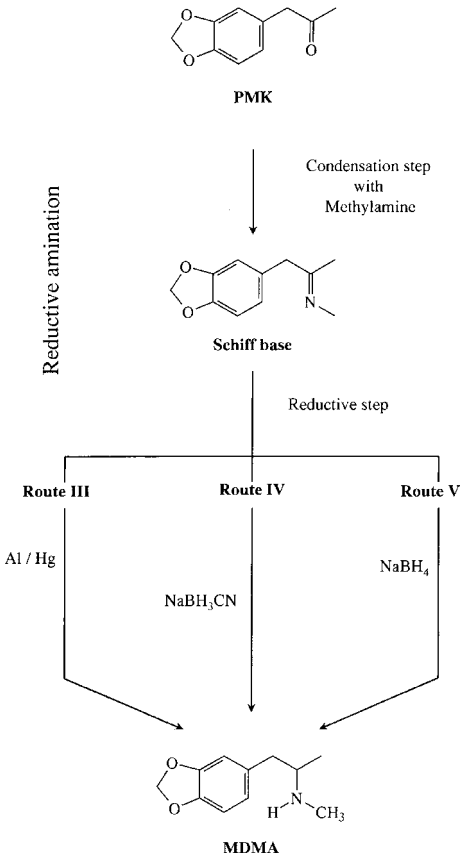


Fig. 2. Chromatograms obtained for PMK samples. (a) Route II, (b) Route I.



Scheme 6.



Scheme 7.

isosafrol oxidation and 20ket is explained by a pinacolic rearrangement of the intermediate isosafrol glycol (Scheme 6), whereas for Route II, origins have been expressed hereabove (Section 3.1.3.). The detection in PMK samples of impurities corresponding to the reduction of safrol/isosafrol and piperonal (impurities 10meth and 11meth) is not yet clear.

3.2. Study of MDMA

MDMA was obtained by reductive amination of PMK, using three different reducing agents (Scheme 7). Starting from the same PMK, first, the imine bond of the intermediate Schiff base formed with methylamine was reduced via an aluminium–mercury amalgam (Route III). Then, metal hydride reduction was tested with sodium borohydrate (Route IV) and the more selective reducing agent cyanoborohydrate (Route V).

On the other hand, in order to compare the influence of precursors used in Routes I and II and to determine the pathway followed by the impurities previously identified, PMK produced via Routes I and II was converted into MDMA via the same route (Route III).

3.2.1. Syntheses

3.2.1.1. Route III. A solution of 0.12 g of $HgCl_2$ in 160 ml water was added dropwise to 5.1 g of a commercial aluminum foil, cut into 2 cm squares. The mixture was cooled and swirled occasionally during addition. After a few minutes, the solution was decanted and the amalgamated foil washed with 200 ml (4×) of water. To the amalgam was then added: 7.6 g of methylammonium chloride in 8 ml water, 23 ml of isopropanol, 18.3 ml of 25% sodium hydroxide solution and 6.75 g of PMK diluted in 45 ml isopropanol. The mixture was stirred for 2 h with temperature kept below 50 °C and then filtered through celite. The filter cake was washed with methanol. The filtrate was concentrated by rotary evaporation and the residue obtained was dissolved in 480 ml of water. After addition of hydrochloric acid (32%) to form MDMA hydrochloride, excess PMK was removed by extraction with methylene chloride. The acidic layer was then basified with 30% sodium hydroxide and the liberated base was extracted with methylene chloride. The organic solution was dried, filtered and concentrated by rotary evaporation. The crude base was purified by low-pressure distillation to yield 3.45 g (47%) of colorless oil.

MDMA hydrochloride was then obtained as white crystals with dissolving MDMA base in cooled isopropanol and acidifying with concentrated hydrochloric acid.

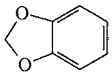
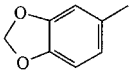
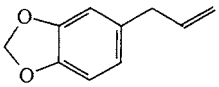
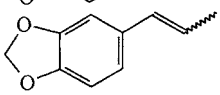
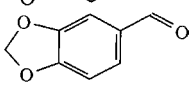
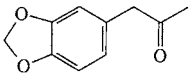
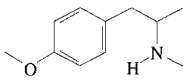
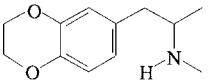
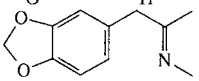
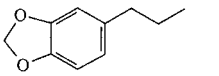
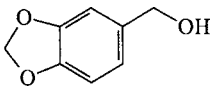
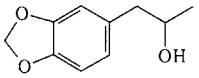
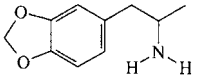
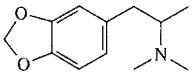
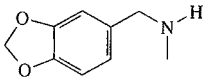
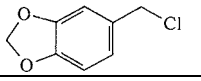
3.2.1.2. Route IV. Under nitrogen atmosphere, to a solution of 2.5 g of PMK and 9.4 g of methylammonium chloride in 50 ml of methanol, was added 1.2 g of sodium cyanoborohydride. The resulting mixture was stirred for 8 h (with periodical additions of concentrated hydrochloric acid to keep pH between 5 and 6) and then added to 600 ml of dilute hydrochloric acid. The acidic layer was treated as in Route III to provide 1.3 g (45%) of MDMA base. Crystallization of the hydrochloride salt was then done as previously.

3.2.1.3. Route V. Under magnetic stirring, a solution of 1.8 g of solid sodium hydroxide in 35 ml of methanol was added to a mixture of 3 g of methylammonium chloride in 25 ml methanol, cooled at −20 °C (ice bath + NaCl). To the obtained methylamine were then added at 5 °C, portionwise, 0.46 g of sodium borohydride. The reaction mixture was then stirred for 7 h with external cooling to keep the temperature below 10 °C. After hydrolysis with dilute hydrochloric acid, acidic layer was treated as in Route IV to provide 2.4 g (48%) of MDMA base. Crystallization of the hydrochloride salt was then done as previously.

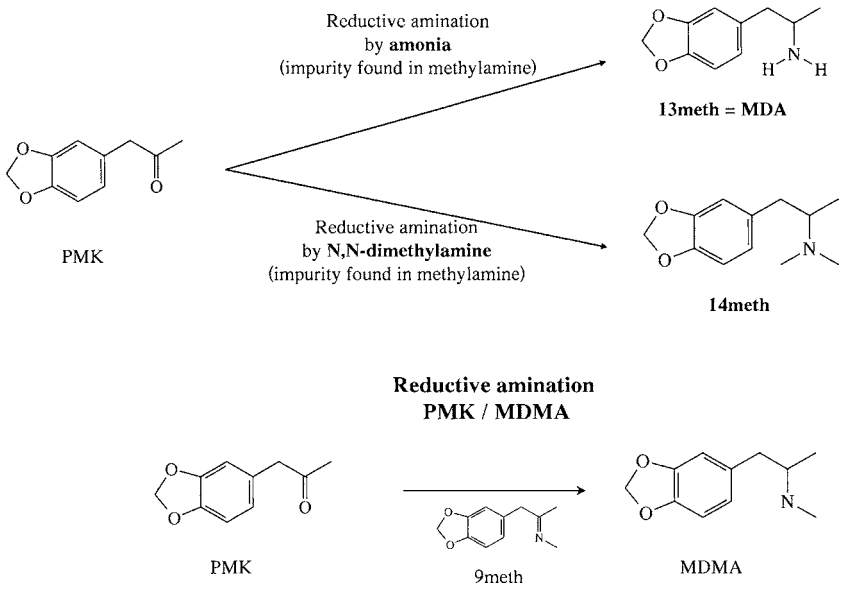
3.2.2. Analysis of MDMA samples

Sixteen characteristic impurities were detected in the MDMA samples (Table 6). Among them, 9meth is the reductive amination route specific impurity.

Table 6
Impurities found in all MDMA samples synthesized from isosafrol depending on the synthesis route

Identification number	*m/z*	Structure	Name	Route I	Route II	Chemical origin
1	121/122,63/64		1,3-Benzodioxole, MW 122	++	++	Impurity found in all samples (from sassafras oil to MDMA)
2	135/136,78/77, 51		3,4-Methylenedioxy toluene, MW 136	++	++	Impurity found in all samples (from sassafras oil to MDMA)
3saf	162, 104, 131, 77, 51		Safrol, MW 162	++	++	Precursor
4iso	162, 104, 131, 77, 51		Isosafrol, MW 162	++	++	Precursor
5kpt	149/150,121, 63, 91		Piperonal, MW 150	++	++++	Oxidation of isosafrol (Route I) or precursor (Route II)
6ket	135, 178, 77, 51, 43		PMK, MW 178	++	++	Intermediate
7meth	58, 121, 78, 91		*p*-Methoxymethamphetamine (pMMA), MW179	++	+	Reductive amination of 9Ket by methylamine
8meth	58-152-56		*N*-Methyl-1-[1,2-dimethoxy-4-(2-aminopropyl)]benzene, MW 209	++	Ø	Reductive amination of 15Ket by methylamine
9meth	56, 191, 135, 77		1,2-(Methylenedioxy)-4-(2-*N*-methyl-iminopropyl) benzene, MW 191	++	++	Intermediate (amination of PMK)
10meth	135, 164, 77, 51		3,4-Methylenediox yphenylpropane (Dihydrosafrole), MW 164	++	++	Reduction of safrol or isosafrol
11meth	152, 135, 93, 65, 123		Piperonyl alcohol, MW 152	++	++	Reduction from piperonal
12meth	135/136, 180, 77, 106, 51, 45		1-(3,4-Methylenedioxy) phenyl-propan-2-ol, MW 180	++	++	Reduction of PMK
13meth	44, 135/136, 77		3,4-Methylenediox yamphetamine (MDA), MW 179	++	++	Reductive amination of PMK by ammonia (impurity found in methylamine)
14meth	72-56-44-73-58-70		*N*,*N*-Dimethyl-3, 4-methylenedioxy amphetamine, MW 207	++	++	Reductive amination of PMK by dimethylamine (impurity found in methylamine)
15meth	135/136,164/165, 44, 77		3,4-Methylenedioxy benzyl-*N*-methylamine, MW 165	++	++	Reductive amination of piperonal by methylamine
16meth	135, 77, 51, 170		Piperonyl chloride, MW 170	++	++	Unknown

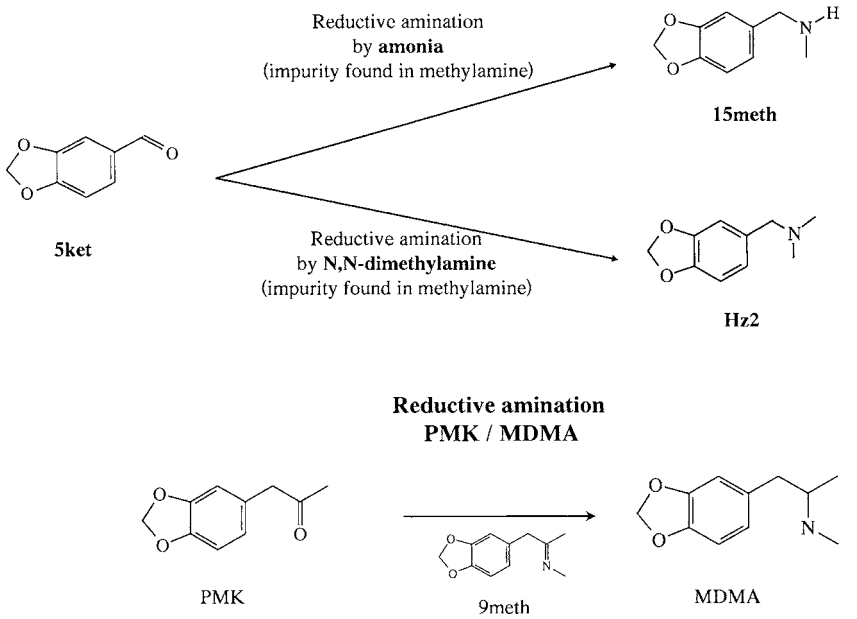
3.2.2.1. Chemical origin and pathway. As reported in Table 6, the impurities 1 and 2 remain unchanged during the different synthesis steps. Nevertheless, it is possible that these two compounds are artefacts produced in the injection port of the gas chromatograph but this hypothesis has not yet been confirmed. Some other compounds are precursors and intermediates (3saf, 4iso, 6ket and 9meth), and their corresponding reductive form (10meth and



Scheme 8.

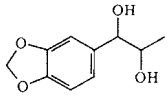
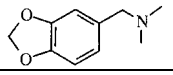
12meth). The origin of impurity 5ket (piperonal) and, therefore, its corresponding reductive form 11meth, has been explained earlier.

The last impurities are final by-products (7meth, 8meth, 13meth, 14meth and 15meth). Some of them (13meth, 14meth, and 15meth) come from a reductive amination of precursors by methylamine or its own impurities (ammonia, *N*,*N*-dimethylamine). Thus, 13meth and 14meth are obtained by a reductive amination of PMK with ammonia and *N*,*N*-dimethylamine, respectively (Scheme 8). Impurities 15meth and Hz2 (see Table 7) come from the same reductive amination but on piperonal (Scheme 9). Attention must be given to impurity Hz2, as this compound, when detected, was only present in MDMA sample synthesized



Scheme 9.

Table 7
Other impurities rarely found in MDMA samples

Identification number	*m/z*	Structure	Name	Note
Hz1	93, 151, 65, 123, 152		Isosafrol glycol, MW 196	
Hz2	135, 58, 179, 77		3,4-Methylenedioxy-*N*, *N*-dimethylbenzene, MW 179	

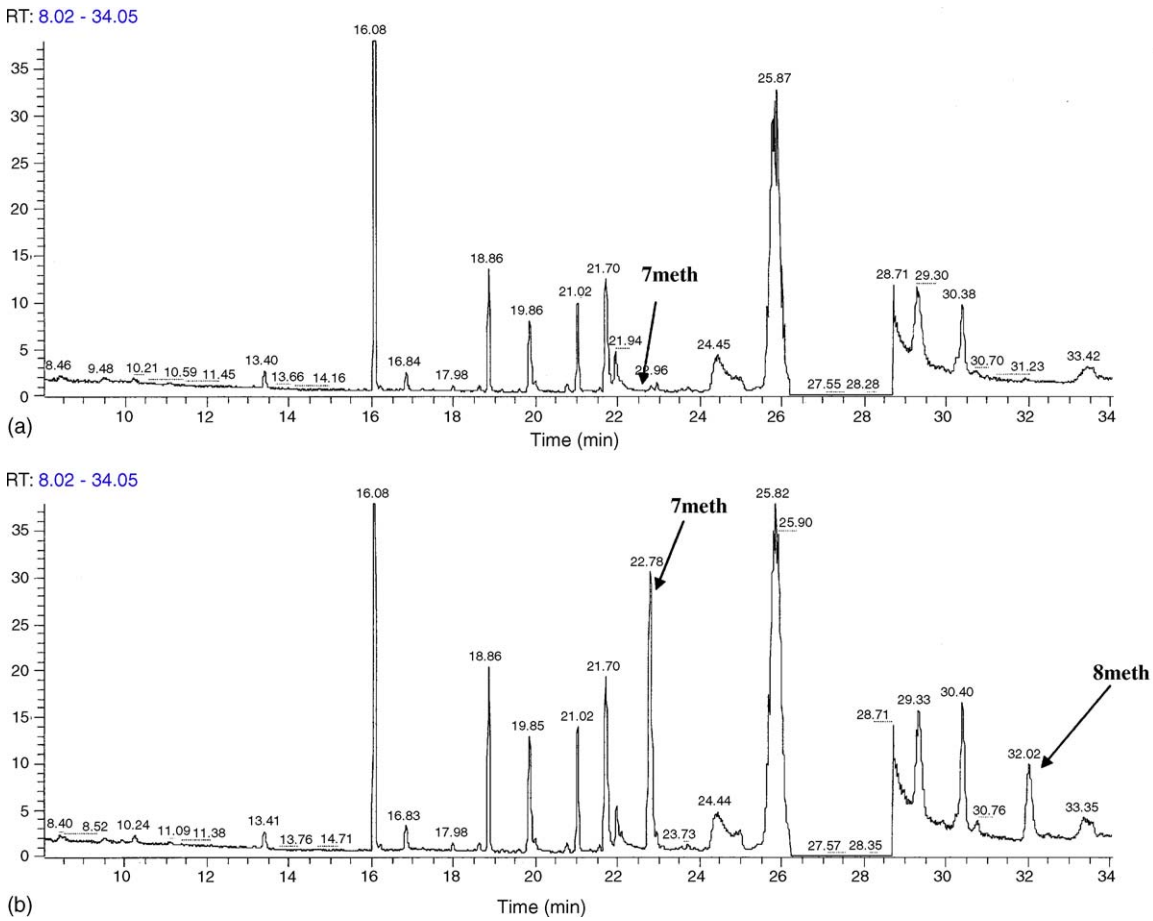


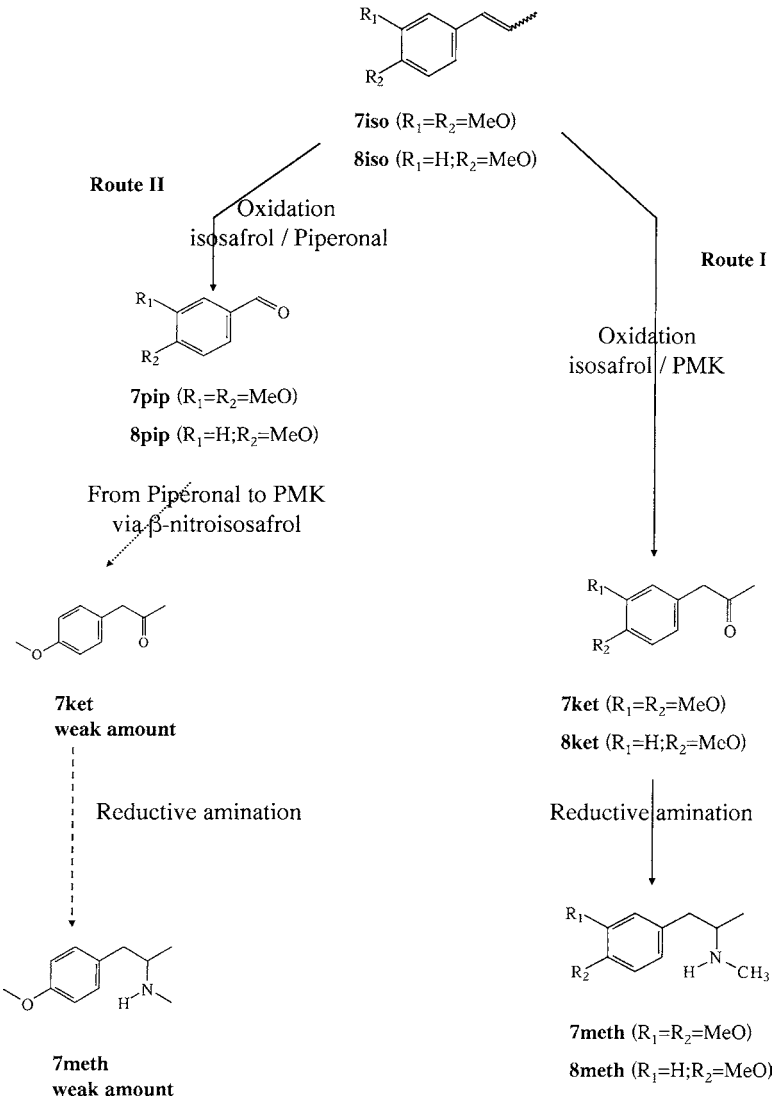
Fig. 3. Chromatograms obtained for MDMA samples. (a) Route II, (b) Route I.

from piperonal (Route II). However, it was not detected in all piperonal made samples.

Impurities 7meth and 8meth come from reductive amination of 7ket and 8ket, respectively, whom origin has been explained earlier.

Finally, impurity 16meth was noticed in all MDMA samples as well as in MDMA tablets. Trying to identify the source of chloride, we substituted the hydrochloride salt by the phosphate one during the crystallization step but it did not eliminate this compound. Therefore, another source of chloride was concerned but not yet identified, maybe the methylamine.

3.2.2.2. Differentiation between Routes I and II. Obviously, discrimination would be easily done by the detection of both ''route specific'' impurities, i.e. isosafrol glycol



Scheme 10.

(Hz1) and the oxime intermediate (21nitro) (Tables 4 and 7). Unfortunately, both compounds were rarely detected in MDMA samples, and even PMK ones, due to their low amount and their bad chromatographic resolution. Hz2, which was only detected in MDMA Route II samples, could also be used to discriminate the routes but is not systematically present.

Therefore, it is necessary to rely on impurities 7meth and 8meth. As we can notice in Fig. 3, in chromatogram (Route II sample), the peak corresponding to 8meth is not present and the one corresponding to 7meth is extremely weak. This has been observed for all Route II samples. As discussed earlier, these impurities are final products coming from 7iso and 8iso, which follow a three-steps synthesis for Route II and a single step synthesis for Route I (Scheme 10). The increase in the number of steps means a decrease of their amounts.

3.2.2.3. Differentiation between Routes III, IV, V. Unfortunately, all the impurities previously described are present (in various amounts) whatever is the reducing agent used (Fig. 4). It points out that it is not possible to make qualitative differences between the three different reduction methods. Moreover, preliminary studies show that semi-quantitative comparison does not improve the discrimination.

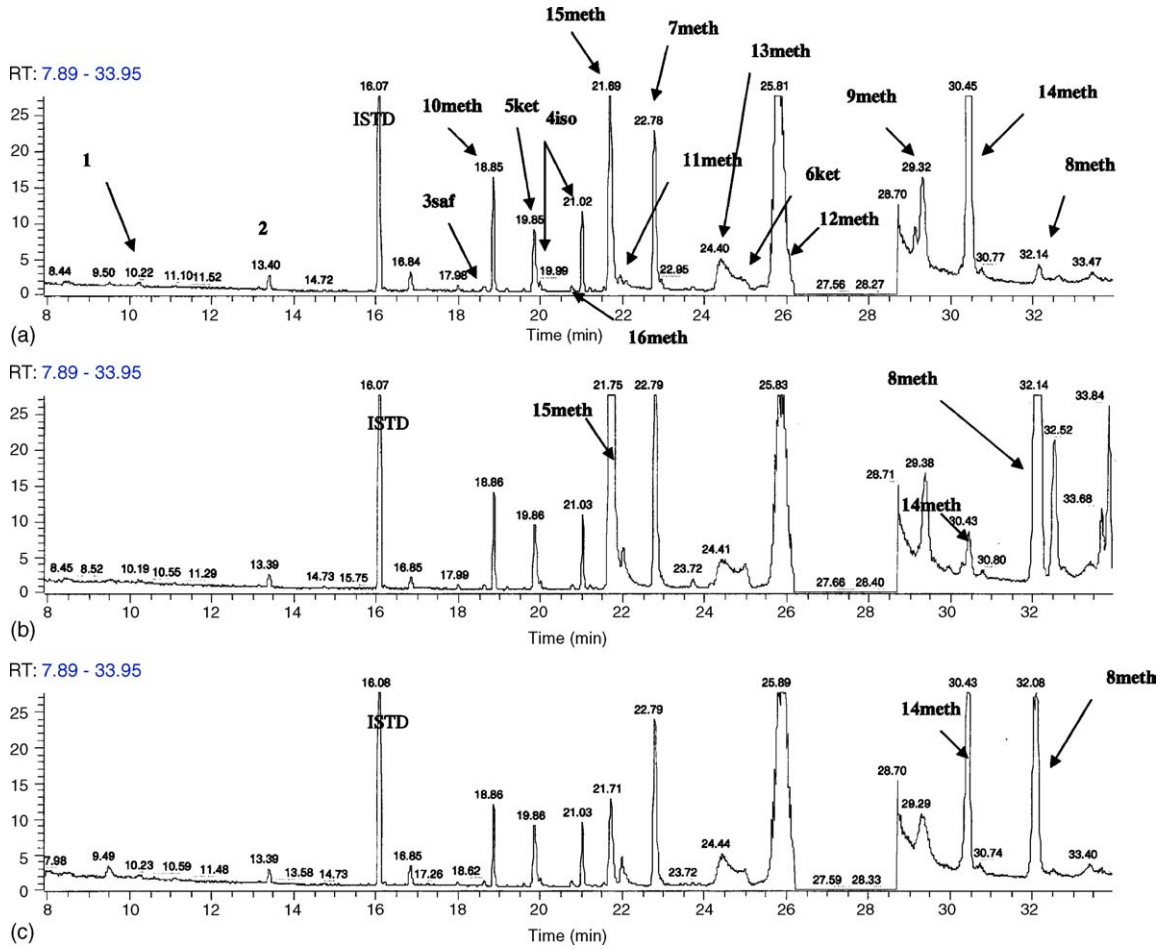


Fig. 4. Chromatograms obtained for the MDMA samples. (a) Route III, (b) Route IV, (c) Route V.

4. Conclusion

The purpose of this article was to present all the impurities found in precursors, intermediates and final products during the synthesis of MDMA from isosafrol via reductive amination. The chemical origin of these impurities was discussed depending on the synthesis routes used.

Differentiation between precursor's sources is possible on the raw materials, but these differences disappear as the chemical process leading to MDMA goes on. Similarly, in spite of the 16 various impurities found in the MDMA samples obtained from the same PMK by three different reduction methods ($NaCNBH_3$, $NaBH_4$, or Al–Hg), no qualitative differences can be noticed between the chromatographic profiles. Other methods such as IRMS (Isotope Ratio Mass Spectrometry), which determines the nitrogen isotope ratio of MDMA, could maybe allow this differentiation [15].

Finally, it seems only possible to discriminate two main routes for PMK and MDMA samples: isosafrol glycol and β-nitroisosafrol thanks to some specific impurities. However, it is necessary to confirm these results on a larger number of samples.

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