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Impurity profiling of seized MDMA tablets by capillary gas chromatography

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Abstract Impurity profiles of 3,4-methylenedioxyethylamphetamine (MDMA) tablets seized in France have been examined. The samples were extracted with methylene chloride under basic conditions and then analyzed by capillary gas chromatography. Almost 30 compounds were identified as precursors, intermediates and by-products. Palmitic and stearic acid were also found as tableting materials. The comparison of the different profiles obtained by the reported procedure provided very useful information about the synthetic processes used by clandestine laboratories and enabled a classification into several groups of profiles. According to these results, the reductive amination route appears to be the most common synthetic pathway in Western Europe. Furthermore, 3,4-methylenedioxyphenyl-2-propanone seems to be the most used precursor in clandestine laboratories.

Keywords 3,4-Methylenedioxyethylamphetamine · MDMA · Impurity profiling · Gas chromatography · GC-MS

Introduction

3,4-Methylenedioxyethylamphetamine (MDMA, ecstasy) is becoming a major drug of abuse in Europe. Prohibited since 1986, MDMA appeared in the French Customs statistics only in 1989, when 3000 tablets were seized. From that time, ecstasy traffic has constantly increased and annual seizures have exceeded one million tablets since 1998. Currently, the use of ecstasy prevails over all other

synthetic drugs in France. Thus, amphetamine, which still represented 80% of synthetic drugs analyzed in 1998 by Customs laboratories, comprised only 4% of such analyses in 2001. At the same time, MDMA increased from 17% to 89% while the total number of amphetamine-like samples rose by 72% [1]. During the same period (1998–2001), cannabis analyses decreased by 14% while cocaine samples increased by more than 43%. After a large decrease in heroin samples (–60%) from 1996 to 1999, analyses again reached the level of 1998 last year.

Concerning the quantity of seized ecstasy, France is second in Europe, just behind the Netherlands, with 25.4% of the seized tablets [2]. MDMA is often produced as the hydrochloride salt and almost invariably in tablet form. The mean purity is around 28% for tablets weighing on average 270 mg (about 75 mg of MDMA per tablet). Starch lactose and other sugars are the main cutting agents, and additional caffeine is sometimes encountered. Seized tablets can be white or colored, sometimes divisible by two and more rarely by four. They are often branded with a logo; the most common is the Mitsubishi logo (three diamonds). The others refer to a trademark (such as Ferrari, Motorola, Playstation or CK), to animals (like lions or birds) or to characters (for example Superman, Batman or Harry Potter).

Many papers have been published on the profiling of amphetamine [3, 4, 5, 6, 7, 8, 9], methamphetamine [10, 11, 12, 13, 14, 15], cocaine [16, 17, 18] and heroin [19, 20, 21, 22]. For MDMA, some workers have reported impurities or by-products [23, 24, 25, 26, 27, 28, 29, 30, 31], and techniques like Raman spectroscopy [32] or isotope ratio mass spectrometry [33] have been used to link seized tablets.

MDMA produced in clandestine laboratories often contains impurities due to the manufacturing process. The presence of these impurities can be a good way to compare different seizures and to establish links between tablets with identical chromatographic profiles. Indeed, material stemming from the same manufacturing batch should have identical impurities in similar relative amounts. Likewise, different production batches from the same lab-

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oratory should certainly be related by similar profiles whereas unrelated seizures are expected to show major differences [34].

In order to validate profiling as a useful method for identifying common manufacturing bases, a preliminary study of profiling of MDMA tablets seized in France has been conducted to establish whether these parameters can be used to imply a common history (synthesis, operating conditions, etc.) without *a priori* knowledge.

Materials and methods

Materials and reagents

The 52 samples of ecstasy (MDMA) tablets presented in the study are representative of seizures made by the French Customs between 1999 and 2000, generally during routine traffic controls. The samples studied correspond to seizures of more than ten tablets from which one or more tablets were randomly chosen.

Ethyl acetate, methylene chloride and *n*-octane were purchased from Carlo Erba, Italy, *n*-hexane and isopropanol from Prolabo, France. All these solvents were of high-pressure liquid chromatography (HPLC) grade. Potassium hydrogencarbonate and potassium carbonate, both of analytical grade, were purchased from Merck, Germany.

Gas chromatography

The gas chromatograph (GC) used was a Varian CP-3800 fitted with a flame ionization detector and equipped with a fused silica capillary column RTX-5MS (30 m×0.25 mm inside diameter and 0.25 µm film thickness). Hydrogen was the carrier gas and the pressure was maintained constant at 10 psi. Samples (1 µL) were injected according to a splitless mode. The injector and detector temperatures were maintained at 270 °C and 280 °C respectively. The column oven temperature was initially set at 80 °C, then ramped at 8 °C/min to 210 °C, then ramped at 25 °C/min to 300 °C and finally held at 300 °C for 5 min in a total run time of 25 min. Samples were injected in duplicate to check repeatability and solvent was injected after each sample as an instrument blank. In order to check instrument performance, a test sample was injected as a reference every 2 days.

Impurity identification was performed by gas chromatography–mass spectrometry using a Hewlett Packard G1800B GCD Electron Ionization Detector. The column, injection mode and chromatographic conditions used were the same as described above for GC-FID analyses.

Sample preparation

The MDMA tablets were crushed and 150 mg of the homogeneous powder was added to 1 mL carbonate buffer at pH 10 (K₂CO₃/KHCO₃; 0.05 M). The suspension was then mixed thoroughly for 5 min. Next, the solution was extracted by vigorous shaking for 5 min with 1 mL of extracting solvent. The organic layer was taken off, filtered, and reduced to a 100-µL volume under dry air before gas chromatography.

Results and discussion

Extraction procedure

In tablets, MDMA and related impurities are present as hydrochloride salts. In order to study the maximum of im-

purities soluble in organic solvents, it was necessary to conduct an extraction after dissolving the tablets under basic conditions.

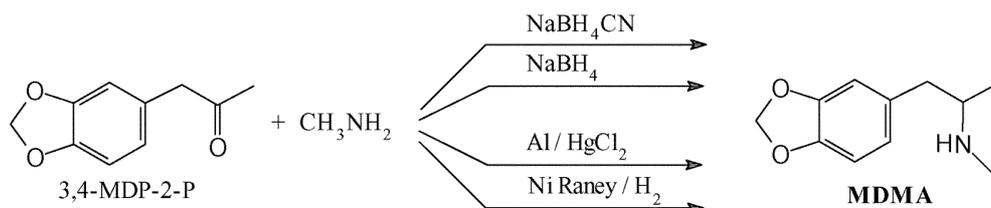
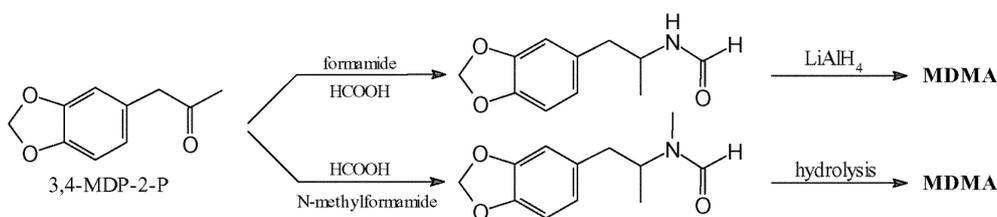
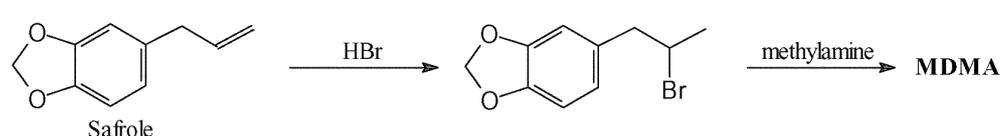
Several extraction solvents were tested: *n*-hexane, *n*-octane, ethyl acetate, methylene chloride and ethyl acetate/isopropanol (50:50 v/v). For each one, a blank extraction was done and presented no significant peaks on gas chromatograms. A comparison of these different solvents showed methylene chloride extraction to be the most efficient. The methylene chloride extract gave more and higher peaks after gas chromatography. Moreover, other solvents led to artefacts, which are undesirable in profiling analyses. As a result, the extractions were carried out with methylene chloride in the subsequent experiments.

The repeatability of this method was ensured by triplicate extractions of large homogeneous samples. Triplicate injections of each extraction were made. For these nine chromatograms, retention times were strictly similar and variations in peak height and area were less than 3%. The stability of the composition of tablets was also examined after storing homogenized powder in darkness at room temperature. Impurity profiles were similar in every respect after 8 weeks of storage.

Impurity profiles

In order to draw conclusions from the presence or absence of impurities in tablets, an understanding of commonly used MDMA synthetic pathways is essential. Synthetic methods using 3,4-methylenedioxyphenyl-2-propanone (3,4-MDP-2-P) seem to be those most likely to be used in clandestine laboratories. These methods are generally simple techniques and require little knowledge of chemistry. Six synthetic pathways using this precursor have been reported [27, 28, 29, 35, 36] as being used for making illicit MDMA. These syntheses, described in Figs. 1 and 2, involve methylamine or formamide as reagents. Four possible synthetic pathways of reductive amination (Fig. 1) use methylamine hydrochloride or methylamine solution. The Leuckart reaction (Fig. 2) seems to be the most common in clandestine amphetamine laboratories. In the case of MDMA, formamide and *N*-methylformamide are commonly used for illicit manufacturing. Other syntheses use safrole as starting material (bromopropane route, Fig. 3). This is relatively inexpensive and available from the distillation of essential oils like saffras oil. After bromination, the intermediate obtained can react with methylamine to give MDMA [37]. Safrole can also be used to obtain 3,4-MDP-2-P after isomerization to isosafrole.

Some impurities found in MDMA samples are reported to be specific to only one pathway [36]: *N*-formyl-MDMA for the Leuckart reaction and bromo compounds for the bromopropane route for example. For the great majority, however, impurities are often common to different processes. Thus, in MDMA profiling, the distribution of all of the impurities can give more important information than specific impurities.

Fig. 1 Possible pathways for the reductive amination route**Fig. 2** Leuckart reaction for MDMA synthesis**Fig. 3** Bromopropane route using safrole as a precursor

It is generally accepted that impurity profiles of synthesized compounds particularly depend on the temperature and time of reaction, the purity of starting materials, and the purification process used for the final product [34]. Furthermore, the material used and the care taken during the synthesis play an important part in the observed impurities.

Results for seized samples

Impurity profiles of 52 3,4-methylenedioxyamphetamine samples seized by French Customs were carried out. Typical chromatograms obtained with seized materials are given in Fig. 4.

During this study, about 30 different products were identified by gas chromatography–mass spectrometry in the analyzed samples. Precursors, amphetamine-like compounds and other impurities are shown in Table 1 with main mass peaks and relative intensities. Relative structures are presented in Fig. 5. These compounds are reported by increasing retention time. Other than precursors, amphetamine-like compounds and synthesis by-products that will be discussed later, we found different phthalates and also fatty acids added as a lubricant to form tablets with MDMA and sugars for example.

Precursors

The most common impurity found is 3,4-MDP-2-P: compound no.°10. Thus, 75% (39) of analyzed samples contained this important product, confirming that MDMA syntheses based on this precursor are those most used by clandestine laboratories in Western Europe.

Isosafrole is also encountered in some samples; this product can be used as a starting material to synthesize directly MDMA or to obtain 3,4-MDP-2-P. In the samples studied, 3,4-MDP-2-P was often present with isosafrole, confirming the use of isosafrole as a precursor of this ketone. It is interesting to note that, when present, only traces of this precursor were observable, indicating a good yield of the first synthetic step or, more probably, a purification before the second step.

Impurities relative to reductive amination

With 3,4-MDP-2-P, the corresponding alcohol, 3,4-methylenedioxyphenyl-2-propanol, is also often present as a byproduct of different manufacturing processes.

3,4-Methylenedioxyphenyl-2-propanol (no.°12), observed in several different samples, seems to be characteristic of the final step of the different “reductive amination” pathways. This alcohol can also be found with syntheses using the “bromopropane route”, but no brominated compound [25, 38] was found in the samples studied. Chromatograms *a* and *b* in Fig. 4 represent samples containing this characteristic alcohol and so are likely to be reductive amination samples. The manufacturing processes used for these samples are very similar and the differences observed are probably due to operating conditions.

Part *c* of Fig. 4 presents other interesting impurities; 3,4-methylenedioxy-*N*-methylbenzylamine and *N,N*-dimethyl-MDA, compounds no.°7 and no.°17. These impurities have also been reported as being linked with the reductive amination process [29, 36]. Their presence is a good way of noting the differences that can occur between the different possible pathways for this reaction (see Fig. 1).

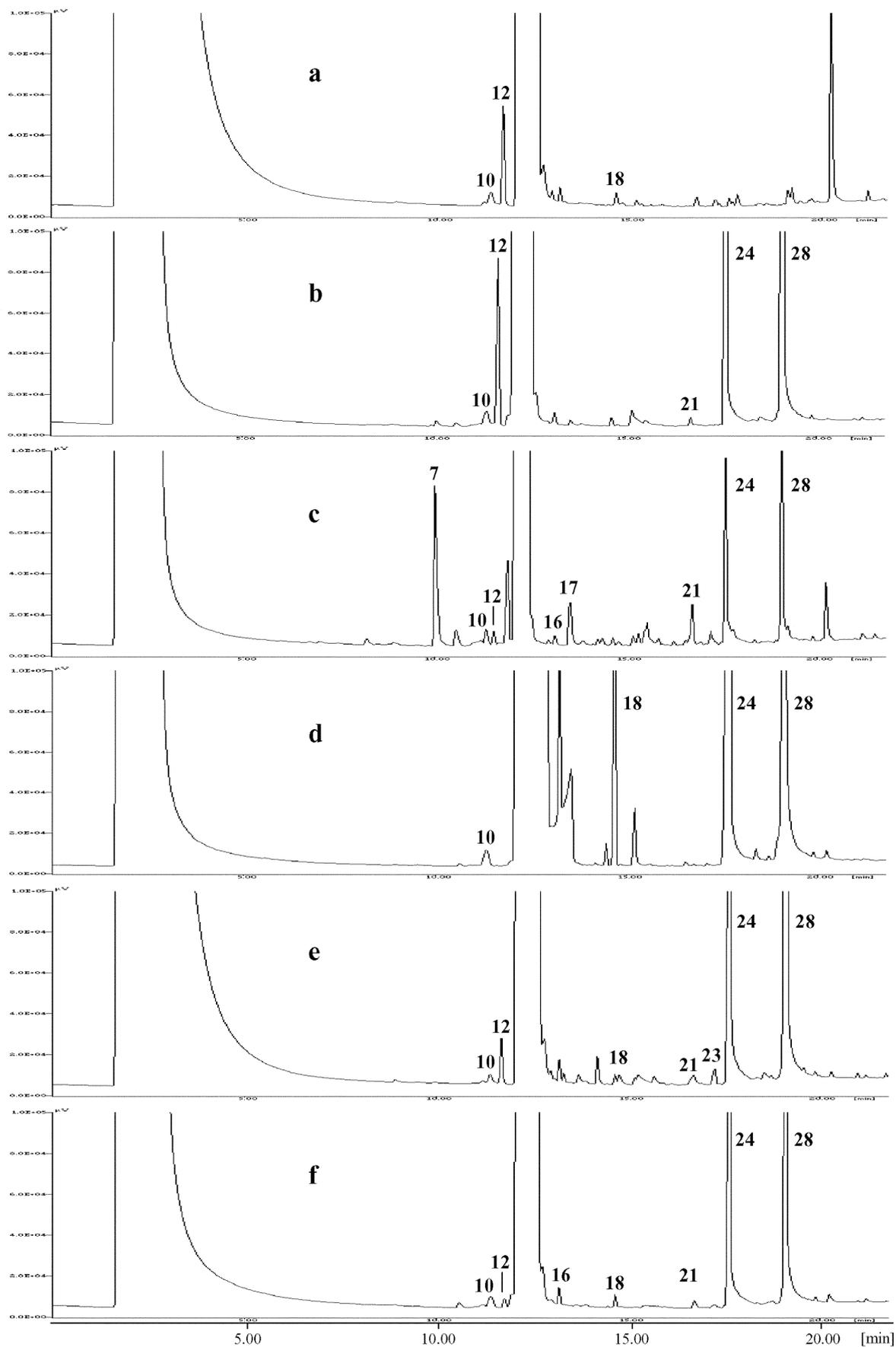


Fig.4 Typical impurity profiles of different MDMA samples. Numbered peaks refer to compounds presented in Table 1. Peak at $R_t=12.2$ min corresponds to MDMA. All parts have the same scale

Table 1 Impurities found in MDMA samples, reported by increasing retention time

No.°	Name	Type of impurity	Mass peaks/intensity				
1	Amphetamine	Amphetamine-like drug	44	91	65	115	120
			100	68	25	18	16
2	Methamphetamine	Amphetamine-like drug	58	91	150	56	65
			100	21	17	11	10
3	<i>N</i> -Ethyl-amphetamine	Amphetamine-like drug	72	44	91	65	73
			100	28	24	8	5
4	Safrole	Precursor	162	163	131	104	135
			100	18	14	9	9
5	Piperonal	Precursor	149	150	121	65	63
			100	86	26	17	16
6	Isosafrole	Precursor or intermediate	162	163	131	104	135
			100	18	14	9	9
7	3,4-Methylenedioxy- <i>N</i> -methylbenzylamine	Byproduct	135	165	164	51	77
			100	60	60	25	20
8	4-Methoxy- <i>N</i> , α -dimethyl-benzeethanamine	Byproduct	58	121	78	42	91
			100	10	5	4	3
9	4-Methyl-5-phenyl pyrimidine	Byproduct	170	169	115	102	171
			100	72	23	21	12
10	3,4-Methylenedioxy-phenyl-2-propanone (3,4-MDP-2-P)	Precursor or intermediate	135	178	77	136	79
			100	39	18	18	10
11	3,4-Methylenedioxy-amphetamine (MDA)	Amphetamine-like drug	136	44	135	137	77
			100	52	17	10	6
12	3,4-Methylenedioxy-phenyl-2-propanol	Byproduct	135	136	180	77	106
			100	88	66	16	9
13	<i>N</i> -Formyl-amphetamine	Intermediate in amphetamine synthesis	132	56	91	115	65
			100	99	77	25	23
14	<i>N</i> -Formyl-methamphetamine	Intermediate in methamphetamine synthesis	86	58	91	118	56
			100	43	10	9	5
15	Diethylphthalate	Binder for tableting	149	176	177	150	121
			100	25	19	13	9
16	<i>N</i> -Ethyl-3,4-MDA (MDEA)	Amphetamine-like drug	72	44	135	136	77
			100	44	7	4	4
17	<i>N,N</i> -Dimethyl-MDA	Byproduct	72	56	44	73	58
			100	11	10	10	5
18	1-(1,2-Dimethyl-1-azacyclopropyl)methyl-3,4-methylenedioxybenzene	Byproduct	190	148	147	188	205
			100	61	40	34	23
19	Tetradecanoic acid	Lubricant for tableting	73	43	60	41	55
			100	97	92	91	75
20	Dibutylphthalate	Lubricant for tableting	149	150	41	76	104
			100	9	7	6	6
21	Caffeine	Adulterant	194	193	55	109	67
			100	32	28	16	13
22	Lidocaine	Contact impurity	86	58	30	87	42
			100	12	8	5	4
23	<i>N</i> -Formyl-MDMA	Intermediate in Leuckart synthesis	79	61	26	23	17
			100	77	33	29	22
24	Palmitic acid	Lubricant for tableting	87	55	129	41	73
			100	76	70	65	55
25	<i>N</i> -Acetyl-MDA	Byproduct	58	162	100	43	135
			100	49	21	10	8
26	Heptadecanoic acid	Lubricant for tableting	73	43	60	57	270
			100	86	86	68	63
27	Oleic acid	Lubricant for tableting	129	87	55	41	185
			100	89	68	65	50
28	Stearic acid	Lubricant for tableting	87	129	55	185	41
			100	80	70	64	62
29	Cocaine	Contact impurity	82	182	83	94	198
			100	68	39	20	16

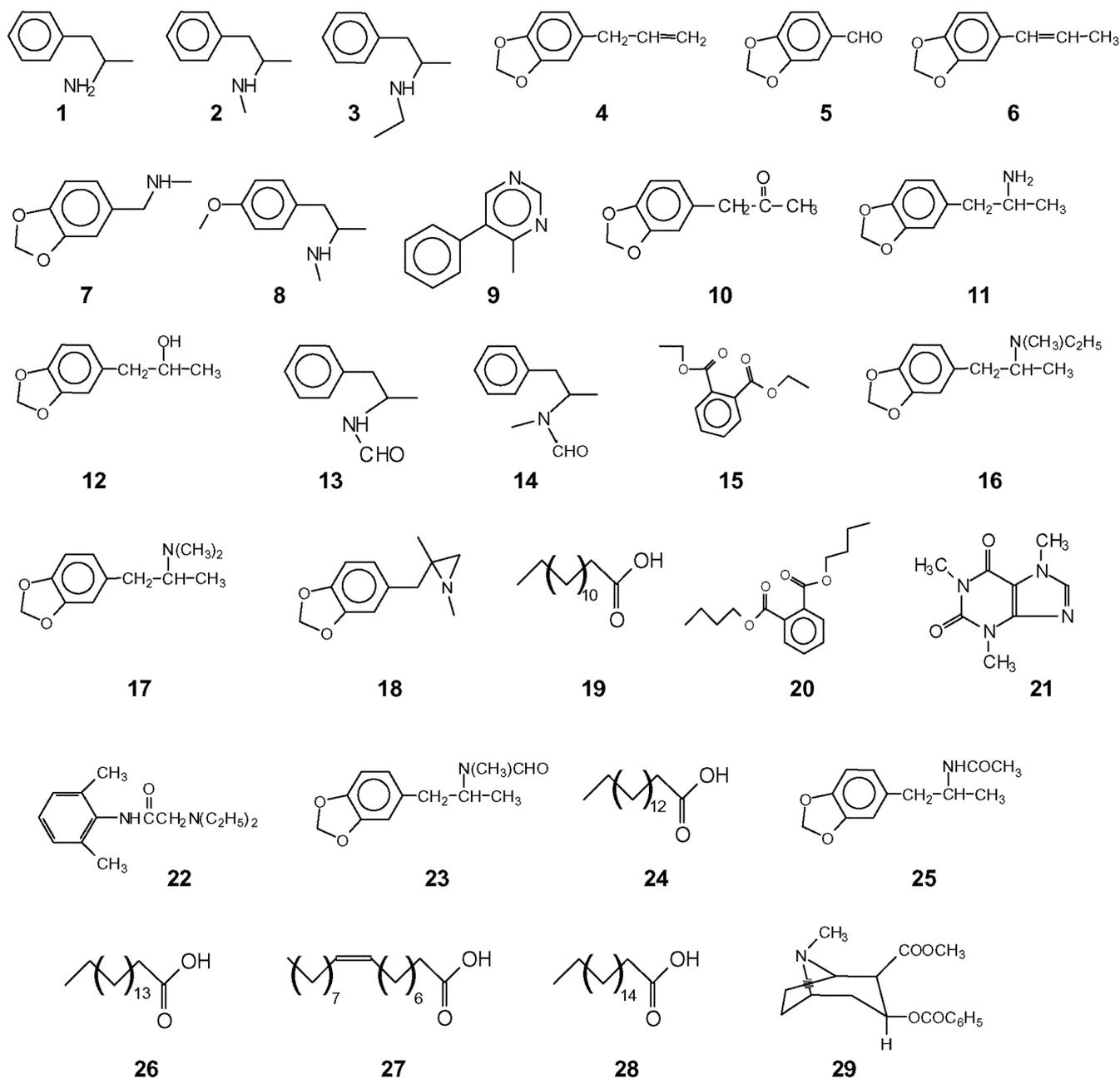


Fig. 5 Structure of impurities found in MDMA tablets. Numbers refer to Table 1

Impurities related to the Leuckart reaction

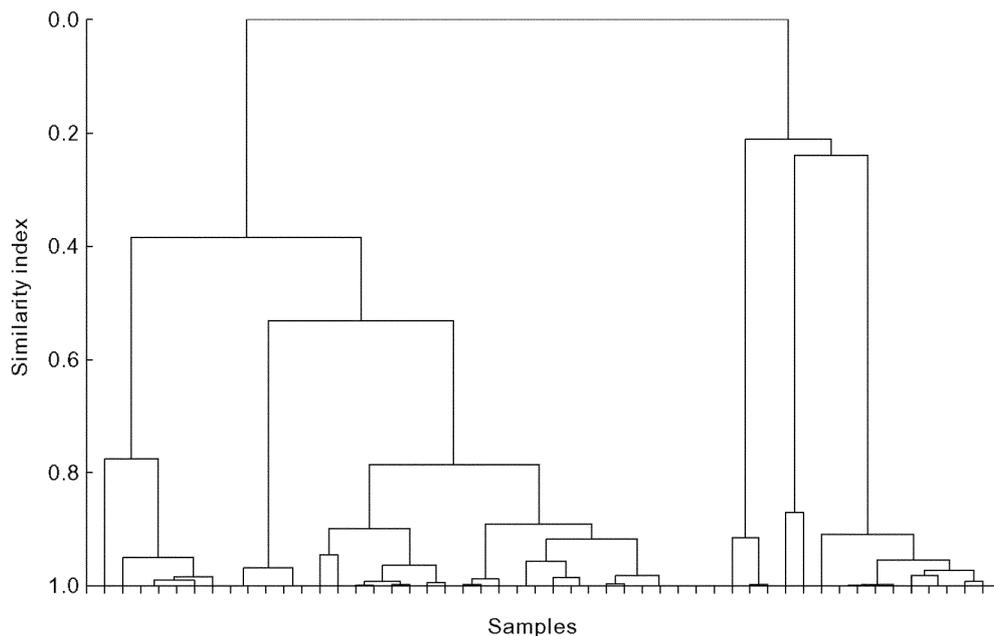
Another interesting impurity found in the samples analyzed is *N*-formyl-MDMA, compound no. 23. This impurity, present in 25% (13) of chromatographic profiles studied, is known to be specific to the Leuckart reaction [36]. Thus, *N*-formyl-MDMA is the only impurity to give precise information about the manufacturing process used (see Fig. 2).

Added compounds

The presence or absence of high peaks of both palmitic and stearic acid was noted. These fatty acids correspond to peaks after 18 min of retention time; the more intense are palmitic (C16) and stearic (C18) acids. Almost 90% of analyzed samples contain these two fatty acids and 80% at high intensity. This criterion only gives information on the tableting process since these products are commonly used as lubricants for "direct compression" to ensure that the powder does not stick to the pressing equipment. Phthalates identified in some samples are also added as a binder before compression.

Caffeine was found in 33 samples, often at a low level. It is added as an adulterant for its CNS stimulant properties. Four samples were also found to contain amphet-

Fig. 6 Dendrogram resulting from the hierarchical cluster analysis of MDMA tablets



amine in addition to MDMA. Cocaine and lidocaine were observed in only one sample, probably as a contact impurity after synthesis.

Comparison of profiles and statistical analysis

As a result of this study, several groups of impurity profiles were established based on the presence and the proportion of impurities discovered. Each group represents at least 10% of the samples analyzed.

The three most important groups are composed of samples containing 3,4-methylenedioxyphenyl-2-propanol (no.°12) for the first two groups and *N*-formyl-MDMA (no.°23) for the third one. These three groups represent 58% of the classified samples. Other samples also contain the alcohol no.°12, but the presence of some weak impurities, probably due to minor modifications in the manufacturing process, led to the creation of the other groups. In these groups, the principal parameters used were the proportion of 3,4-MDP-2-P and 3,4-methylenedioxyphenyl-2-propanol and the presence of 3,4-methylenedioxy-*N*-methylbenzylamine, MDA, MDEA, *N*-acetyl MDMA and *N,N*-dimethyl MDA.

To improve the group classification of subsequent analyses of a large set of chromatograms, statistical methods could be a good approach. For this statistical analysis, all compounds presented in Table 1 were used as variable in a multivariate analysis, except cocaine and lidocaine considered here as contact impurities. The data matrix obtained was examined by hierarchical cluster analysis. Figure 6 presents the dendrogram resulting from this method.

Case studies

We report here two examples of the application of profiling analyses. The first cases linked via impurity profiling concern two seizures of MDMA tablets. In April 2001, 1500 “Euro” tablets were seized in the East of France, near the German border. One month later, in the same area, 750 “Batman” tablets were found, again during a traffic control. There was no particular reason to link these seizures because no similarities were observed in their physical parameters. In addition to their different logos, their masses, diameters, thicknesses and MDMA contents were not comparable. In contrast, the impurity profiles of the two samples were identical (part *d* of Fig. 4), showing that these tablets might well have originated from the same synthetic batch.

Another interesting example concerns four seizures of “Mitsubishi” tablets. These seizures, made between September 1999 and March 2000, contained 52, 3000, 2000, and 200,000 tablets respectively. Physical parameters were used to divide these seizures into two groups of tablets weighing 345 and 285 mg. All the seizures were made in the North of France; two near the Belgian border, one in a train to Paris and the other in a truck, indicated as going to England. These samples were analyzed by chromatography, and the comparison of the four impurity profiles suggests that all the tablets may have come from a single major clandestine laboratory. The four profiles obtained correspond to chromatogram *e* in Fig. 4. Other Mitsubishi tablets seized in the same period in Paris gave profiles similar to part *c* of Fig. 4, showing that this sample might have come from a different network.

These two examples confirm the value of profiling in linking different MDMA seizures. After routine application of this method, analytical conclusions may enable intelligence services to increase their knowledge of clandestine

tine networks. However, the results obtained so far provide only strong indications. Since all the samples analyzed come from Customs seizures, their history and synthesis are difficult to know. Thus, this kind of study should provide more evidence to identify “common-batch” samples.

Conclusion

In this study, 52 impurity profiles of seized MDMA tablets were examined. The extraction procedure, using methylene chloride under basic conditions, provides some specific profiles by capillary gas chromatography. Some of the identified impurities give interesting information about the different synthetic processes used in clandestine laboratories. The great majority of MDMA tablets analyzed originate from one of the different possible reductive amination processes. Thus, 3,4-MDP-2-P is the most important precursor involved in the synthesis of MDMA seized in France. Differences in manufacturing conditions or reagents used lead to a variety of chromatographic profiles. A comparison of the profiles obtained enables samples to be divided into groups according to the probable common or different origins of MDMA.

In order to compare seizures, the construction of a large database is essential. With this aim, the analysis of seized samples is continuing and a comprehensive statistical analysis will be performed as soon as there are sufficient impurity profiles. In addition, different synthetic routes are being explored at the LAIEM in order to link the presence of particular impurities to a specific synthetic pathway. These results will be discussed in a future publication.

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